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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, DC 20549

Form 10-K

(Mark One)

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

For the fiscal year ended December 31, 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)	*(IRS Employer Identification No.)*
88 Sidney Street, Cambridge, MA	**02139**
(Address of principal executive offices)	*(Zip Code)*

Registrant's telephone number, including area code:
(617) 649-8600

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

Title of Class	Trading symbol(s)	Name of Exchange on Which Registered
Common Stock, Par Value $0.001 per share	**AGIO**	**Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☑ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☑

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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☑

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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

The aggregate market value of the voting and non-voting Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant's Common Stock as of June 30, 2022 (based on the last reported sale price on the Nasdaq Global Select Market as of such date) was $1,200,277,504.

As of February 17, 2023, there were 55,285,223 shares of Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2023 Annual Meeting of Stockholders to be filed pursuant to Regulation 14A within 120 days of the end of the registrant's fiscal year ended December 31, 2022 are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

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PART I

References to Agios

Throughout this Annual Report on Form 10-K, "the Company," "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.

Cautionary Note Regarding Forward-looking Information

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans, and objectives of management, are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "goal," "intend," "may," "plan," "potential," "predict," "project," "should," "strategy," "target," vision" "will," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements regarding:

- our plans to commercialize PYRUKYND® (mitapivat);
- the initiation, timing, progress and results of current and future preclinical studies and clinical trials, and our research and development programs;
- the potential of the isoforms of pyruvate kinase, including PKR, as therapeutic targets;
- the potential benefits of our products and product candidates targeting PKR, including PYRUKYND® (mitapivat) and AG-946, and our PAH stabilizer program;
- our plans to develop and commercialize any additional product candidates for which we may receive approval, either alone or with partners;
- our ability to establish and maintain collaborations or to obtain additional funding, if needed;
- the timing or likelihood of regulatory filings and approvals;
- our strategic vision;
- the timing, likelihood and amount of contingent consideration we may receive from Servier Pharmaceuticals LLC, or Servier, in connection with the sale of our oncology business to Servier that we consummated in March 2021;
- the implementation of our business model and strategic plans for our business, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the rate and degree of market acceptance and clinical utility of our products;
- our competitive position;
- our intellectual property position;
- developments and projections relating to our competitors and our industry;
- the impact of the COVID-19 pandemic on our business, operations, strategy, goals and anticipated milestones; and
- our estimates regarding our ability to achieve cash flow positivity, expenses, future revenue, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in this Annual Report on Form 10-K, particularly in the "Summary Risk Factors" and "Risk Factors" sections, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, in-licensing arrangements, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. All of the market data used in this Annual Report on Form 10-K involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. We

believe that the information from these industry publications, research, surveys and studies is reliable. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of important factors, including those described in the sections titled "Summary Risk Factors" and "Risk Factors."

Summary Risk Factors

Our business is subject to a number of risks that if realized could materially affect our business, financial condition, results of operations, cash flows and access to liquidity. These risks are discussed more fully in the "Risk Factors" section of this Annual Report on Form 10-K. Our principal risks include the following:

- If we do not successfully commercialize PYRUKYND® for the treatment of adults with PK deficiency in the approved jurisdictions and other products for which we receive approval, our prospects may be substantially harmed. Our ability to generate product revenue from PYRUKYND® depends heavily on our successful development and commercialization of the product.
- We depend heavily on the success of our clinical product candidates, including, upon approval, 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 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 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.
- The COVID-19 pandemic has and may continue to affect our ability to initiate or continue our planned, ongoing and future preclinical studies, clinical trials, disrupt regulatory activities, disrupt our ability to maintain a commercial infrastructure for PYRUKYND® or have other adverse effects on our business and operations.
- PYRUKYND®, or any of our product candidates that may receive marketing approval in the future, may be less effective than previously believed or cause undesirable side effects that were not previously identified in clinical trials or may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success, which could compromise our ability, or that of any collaborators, to market the product.
- If we are unable to establish and maintain sales and marketing capabilities or enter into agreements with third parties to sell and market our products, we may not be successful in commercializing PYRUKYND® or our product candidates if and when they are approved.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product or our product candidates. 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.
- We are singularly focused on products and product candidates for the treatment of rare diseases. As a result, we may be more susceptible to changing market conditions, including fluctuations and risks particular to the markets for patients with rare diseases, than a more diversified company, which could adversely affect our business, financial condition and results of operations.
- If our existing capital is insufficient to execute our operating plan through major catalysts and to cash-flow positivity, we will need to raise capital, and if we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.
- We have historically incurred operating losses. We expect to incur losses in the future and may never achieve or maintain profitability. Our net loss for the year ended December 31, 2022 was $231.8 million, our net income for the year ended December 31, 2021 was $1,604.7 million and our net loss for the year ended December 31, 2020 was $327.4 million. The net income we generated in the year ended December 31, 2021 was due to the sale of our oncology business to Servier in March 2021. As of December 31, 2022, we had an accumulated deficit of $470.6 million.
- We currently rely and expect to continue to rely on third parties for the manufacture of our product candidates for preclinical and clinical testing and for commercial supply of PYRUKYND® and any product candidate for which we obtain marketing approval. Any performance failure on the part of our existing or future third-party manufacturers could delay clinical development, marketing approval or our commercialization efforts.

- 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 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.
- If we are unable to obtain and maintain patent or trade secret protection for our medicines and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize medicines and technology similar or identical to ours, and our ability to successfully commercialize our medicines and technology may be adversely affected. If we do not, or are unable to, obtain or maintain any issued patents for any of our most advanced product candidates, it could have a material adverse effect on our competitive position, business, financial condition, results of operations, and prospects.

Item 1. Business

General

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 diseases. 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 rare diseases.

Sale of Oncology Business to Servier Pharmaceuticals, LLC (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 U.S. Food and Drug Administration, or FDA, with an approved label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an isocitrate dehydrogenase 1 or 2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), as well as a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity, and a royalty of 15% of U.S. net sales of vorasidenib from the first commercial sale of vorasidenib through loss of exclusivity. The milestone payment for approval of vorasidenib and royalty payments related to vorasidenib and TIBSOVO® represent contingent consideration. 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 $9.9 million and $6.6 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 consolidated statements of operations for the year ended December 31, 2022 and December 31, 2021, respectively.

Sale of Contingent Payments

The consideration for the sale of our oncology business to Servier includes a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity, referred to as contingent payments. We recognize the contingent payments in the royalty income from gain on sale of oncology business line item in our consolidated statements of operations in the period when realizable. On October 27, 2022, we sold our rights to future contingent payments to entities affiliated with Sagard Healthcare Partners, or Sagard, and recognized income of $127.9 million within the gain on sale of contingent payments line item in our consolidated statements of operations for the year ended December 31, 2022. 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 this 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.

Business Overview

Rare diseases

The lead product candidate in our portfolio, PYRUKYND® (mitapivat), is an activator of both wild-type and mutant pyruvate kinase, or PK, enzymes for the potential treatment of hemolytic anemias. In February 2022, the FDA approved PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. In November 2022, we received marketing authorization from the European Commission for PYRUKYND® for the treatment of PK deficiency in adult patients in the European Union, or EU. In December 2022, we received marketing authorization in Great Britain for PYRUKYND® for the treatment of PK deficiency in adult patients under the European Commission Decision Reliance Procedure. 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, or LR MDS, and hemolytic anemias.

In addition to the aforementioned clinical development programs, we continue to invest in our late-stage research program focused on advancing a phenylalanine hydroxylase, or PAH, stabilizer for the treatment of phenylketonuria, or PKU.

With nearly 15 years of focused study in cellular metabolism, we have a deep understanding of this biology, which is involved in the healthy functioning of nearly every system in the body. Building on this expertise, these learnings can be rapidly applied to our clinical trials with the goal of developing medicines that can have a significant impact for patients.

Our Strategy and Long-term Goals

As part of our long-term strategy, we have developed and articulated a strategic vision that delineates our expected evolution in light of our singular focus on rare diseases. We aim to build a sustainable, value-creating company, based on our expertise in cellular metabolism and classical hematology, that develops and delivers differentiated medicines for patients.

By 2026, our vision is to: establish a classical hematology franchise with PYRUKYND® approvals across PK deficiency, thalassemia and SCD; expand our portfolio by advancing AG-946 and our preclinical pipeline as well as through disciplined business development aligned with our core therapeutic focus areas and capabilities; and achieve cash-flow positivity.

Our Core Values

Our company's values cultivate an environment that promotes collaboration, contribution, engagement and high regard for others' points of view. This foundation helps our people push the boundaries of our science and create transformative medicines, which we believe will provide long-term benefits for all our stakeholders. Our connections – with each other and with external parties – fuel the development of new therapies for the people who need them. Our core values include:

- *Aim High:* We set the bar high for ourselves, and we keep working to raise it. At our core, we're guided by a deep respect for the science and a commitment always to act with the utmost integrity.
- *Come Together:* We grow supportive relationships with patients and caregivers. We build trusting connections with collaborators. Together, we make a bigger impact than we ever could alone.
- *Embrace Differences:* Because opportunities and insights come from anywhere and anyone, we honor all voices and encourage honest dialogue. We learn equally from success and failure, bringing an open mind and a flexible approach to everything we do.
- *Bring Your Whole Self:* We know we make the biggest impact when each of us can contribute and lead in our own way.
- *Blaze New Trails:* We ask the tough questions that can lead to groundbreaking scientific advances. We nurture a creative mindset and resourceful approach that spark life-changing innovations for patients.

Cellular Metabolism

Cellular metabolism is involved in the healthy functioning of nearly every system in the body and refers to the set of life-sustaining chemical transformations within the cells of living organisms. The conversion of nutrients into energy via enzyme-catalyzed reactions allows organisms to grow and reproduce, maintain their structures, and respond to their environments. Additionally, metabolites serve as key regulators of diverse aspects of cellular biology, and pharmacologic targeting of metabolism can therefore have disease-modifying effects in a wide variety of pathologies. The chemical reactions of metabolism are organized into metabolic pathways, in which one chemical is transformed through a series of steps into another chemical, by a sequence of enzymes. Enzymes catalyze quick and efficient reactions, serve as key regulators of metabolic pathways, and respond to changes in the cell's environment or signals from other cells. We believe our deep understanding of

cellular metabolism can be rapidly applied to our clinical trials with the goal of developing medicines that can have a significant impact for patients.

Rare diseases

Diseases are typically considered rare if they affect fewer than 200,000 people in the United States, or fewer than five per 10,000 people in France, Germany, Italy, Spain, United Kingdom, or the EU5. Many rare diseases are likely to be under-diagnosed given the lack of available therapies or diagnostics, the rarity of the condition, or limited understanding of how the disease genetics relate to the disease phenotype. It has been shown that small molecule therapies able to specifically correct genetic deficiencies and their associated organ dysfunction may have application in conditions that arise independent of patient genetics but for which identical organ dysfunction occurs. For example, a treatment for a hereditary hemolytic anemia may find direct application in the treatment of a secondarily acquired hemolytic anemia.

Many rare diseases carry severe or life-threatening features. In many of these disorders, the defect of single or multiple genes leads to a deficient expression or function in one or several gene products which collectively manifest in organ dysfunction. As these conditions are by nature congenital and frequently hereditary, they are often detected either by genetic testing or phenotypic diagnosis in newborns or in early childhood. A typical course of many such diseases is inexorable deterioration until death or significant irreversible life-long disability and/or suffering.

Current treatment options for these disorders are generally limited. Severe and sustained diet modification or nutrient supplementation can be beneficial in certain rare diseases. Several of these disorders, from a group known as lysosomal storage diseases, have been treated successfully with enzyme replacement therapy, or ERT, the therapeutic administration of a functional version of the defective enzyme. Examples of ERTs for lysosomal storage disorders include Fabrazyme® for Fabry disease, Myozome® for Pompe disease, Cerezyme® for Gaucher disease, and Elaprase® for Hunter syndrome. In addition, treatment of polygenic conditions such as achondroplasia by Vosoritide® and the monogenic condition, spinal muscular atrophy by gene therapy with Zolgensma® and Spinraza® represent novel technologic approaches to addressing rare diseases.

Most mutations driving rare diseases are intracellular and not amenable to corrective treatment with enzyme replacement therapies. Novel technologic approaches such as gene therapy are also being tested in a minority of conditions and are technologies with limited application based on cost, complexity and patient selection factors. Despite the promising progress made for patients with a small group of rare diseases, the majority of patients with these diseases have few therapeutic options, and the standard of care for many such conditions is palliative, meaning treatment of symptoms with no effect on underlying disease mechanisms. Our goal is to develop mechanistically specific, small molecule approaches with the potential to have disease modifying and long-term rather than palliative effects. We are taking a novel small molecule approach to correct the defects within diseased cells with a goal of developing transformative medicines for patients.

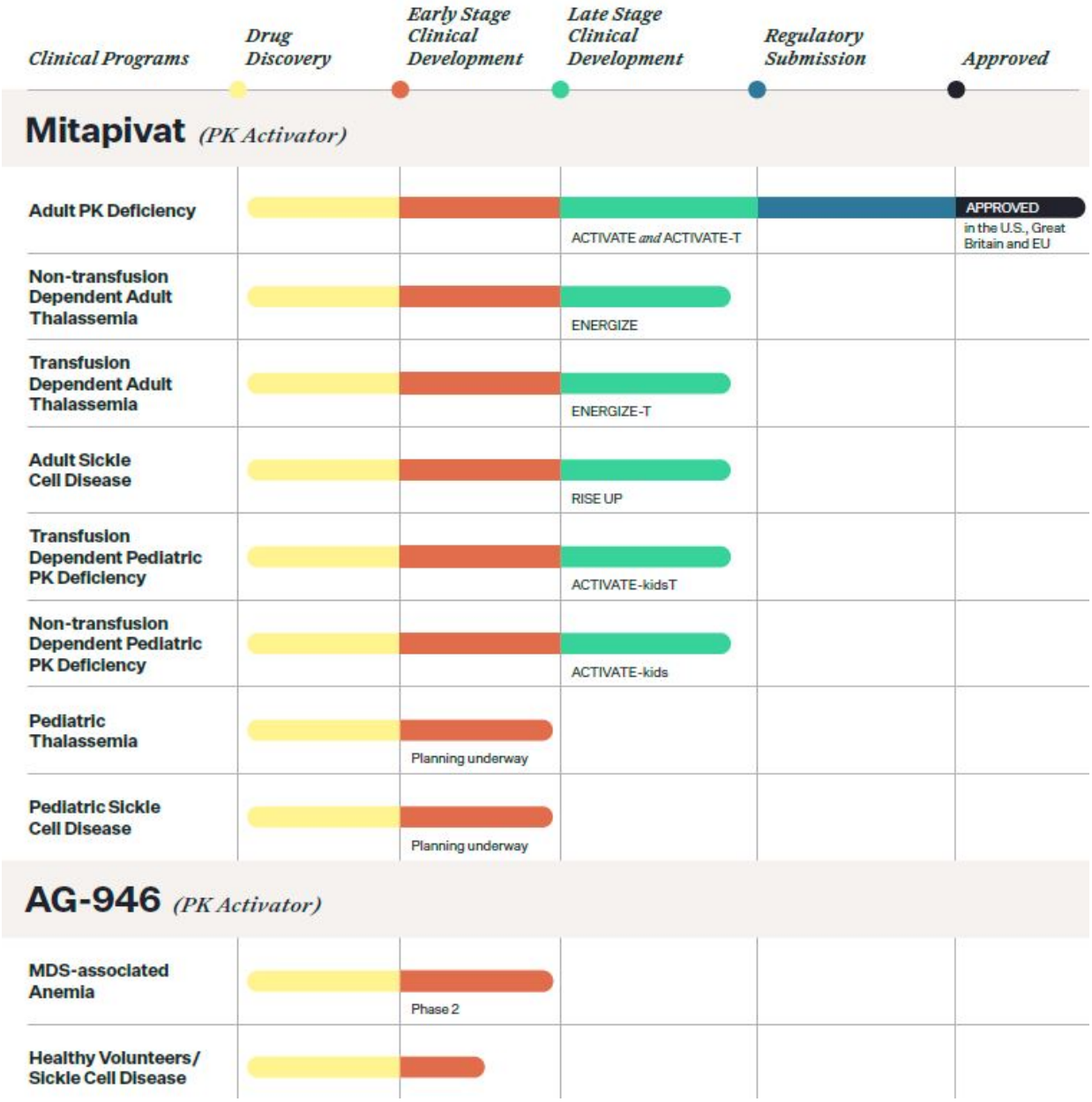
Classical hematology

Classical hematology refers to the study and treatment of blood disorders that are not cancerous, including thrombotic and hemorrhagic disorders, anemia, thrombocytopenia, disorders of iron metabolism and hemoglobin disorders. Many of these diseases are debilitating, have a negative impact on patients' quality of life and are associated with severe complications and/or shortened life expectancy. Despite the significant need for novel therapies and improved patient care, there is a shortage of research and trained specialists in the field of classical hematology, and patients with these disorders are often underserved and experience health disparities and inequity. In addition, even in diseases in which some progress has been made, large subsets of the disease may remain underserved. Our goal is to develop transformative oral treatments for patients with various classical hematological disorders through broad clinical development programs in order to address the unmet needs of a large range of patients.

Our Development Programs

We believe that leveraging our core capabilities in cellular metabolism combined with our singular focus on rare diseases and our differentiated expertise in classical hematology has significantly enhanced our ability to advance new therapeutic candidates and bring innovative medicines to patients in need. We have a proven track record of developing new therapeutic approaches and multiple proprietary first-in-class orally available small molecules.

The following summarizes our approved product and most advanced clinical product candidates, each of which is described in further detail below.



PK Activator Program

PK is the enzyme involved in the second to last reaction in glycolysis — the conversion of glucose into lactic acid. This enzyme has several tissue-specific isoforms (PKR, PKL, PKM1 and PKM2). Pyruvate kinase-R, or PKR, is the isoform of PK that is present in red blood cells, or RBCs. Mutations in PKR cause defects in RBC glycolysis and lead to a hematological rare disease known as PK deficiency. Glycolysis is the only pathway available for RBCs to maintain the production of adenosine triphosphate, or ATP, which is a form of chemical energy within cells. Accordingly, we believe that activation of mutant forms of PKR can restore glycolytic pathway activity and increase RBC health in patients with PK deficiency, and activation of wild-type (non-mutated) PKR can increase ATP which can then meet the increased demands resulting from metabolic stress in RBCs of patients with hemolytic anemias such as thalassemia and SCD.

PK Deficiency

PK deficiency is a rare genetic disorder and disease understanding is still evolving. We estimate that the prevalence of PK deficiency is between approximately 3,000 and 8,000 individuals in the United States and EU5 and we believe that the disease is likely under-diagnosed. PK deficiency leads to a shortened life span for RBCs and is the most common form of non-spherocytic hemolytic anemia in humans.

There is currently no known unique ethnic or geographic representation of the disease. The disease manifests by mild to severe forms of anemia caused by the excessive premature destruction of RBCs. The chronic hemolysis can lead to long-term complications and comorbidities, regardless of the degree of the anemia, often resulting in jaundice and lifelong conditions associated with chronic anemia and secondary complications. The precise mechanism for the hemolysis is not well understood but is thought to result from membrane instability secondary to the metabolic defect caused by the low level of PKR enzyme. The hemolysis is “extra-vascular” in that the RBCs are destroyed in small capillaries or organs and do not spontaneously break open in the circulation. PK deficiency is an autosomal recessive disease whereby all patients inherit two mutations, one from each parent. Children with the disease produce PKR enzyme that has only a fraction of the normal level of activity (generally <50%). Current management strategies for PK deficiency, including blood transfusion and splenectomy, are associated with both short- and long-term risks. More than 350 different mutations have been identified to date. As a result, there are many different possible mutant combinations and no one clear mutational profile. The mutations observed in PK deficiency patients are classified in two main categories. A missense mutation causes a single amino acid change in the protein, generally resulting in some functional protein in the RBCs. A non-missense mutation is any mutation other than a missense mutation, generally resulting in little functional protein in the RBCs. It is estimated that 58 percent of patients with PK deficiency have two missense mutations, 27 percent have one missense and one non-missense mutation, and 15 percent have two non-missense mutations. Boston Children’s Hospital, in collaboration with us, is conducting a Natural History Study to better understand the symptoms and complications of PK deficiency, identify patients and treatment centers, and capture other clinical data, including genetic information. We initiated a global registry, called Peak, for up to 500 adult and pediatric patients with PK deficiency in the first quarter of 2018 to increase understanding of the long-term disease burden of this chronic hemolytic anemia.

Thalassemia

Thalassemia is a hereditary blood disorder in which mutations in the α- or β-globin chains of hemoglobin lead to globin chain precipitates and aggregates that disturb the RBC membrane and induce oxidative stress, leading to decreased survival of RBC precursors, ineffective erythropoiesis, hemolysis of mature RBCs, and anemia. We estimate that the prevalence of thalassemia is between 18,000 and 23,000 individuals in the United States and EU5. In addition to anemia, patients with thalassemia can experience enlarged spleen, bone deformities, iron overload, fatigue, and infection. Current treatment strategies for thalassemia include blood transfusion and bone marrow transplantation, as well as newer therapies such as Reblozyl® for the treatment of β-thalassemia. We believe that the activation of wild-type PKR may increase ATP production and improve red cell fitness and survival of thalassemic RBCs, by increasing the clearance globin chain aggregates through ATP-dependent proteolytic mechanisms.

Sickle Cell Disease

SCD is an inherited blood disorder caused by mutations in hemoglobin that enable the hemoglobin to form long polymeric chains under certain conditions such as low oxygenation, or deoxygenation. Polymerization of this irregular hemoglobin results in RBCs taking on a sickle shape, causing them to aggregate and obstruct small blood vessels, restricting blood flow to organs resulting in pain, cell death and organ damage. We estimate that the prevalence of SCD is between 120,000 and 135,000 individuals in the United States and EU5. RBC deoxygenation is modulated by several factors, including the levels of 2,3-diphosphoglycerate, or 2,3-DPG, which is found to be elevated in sickle cell patient RBCs. Current treatment strategies focus on managing and preventing acute RBC sickling, and include hydroxyurea, L-glutamine and blood transfusions, as well as recently approved therapies such as Adakveo® and Oxbryta®. We believe that activation of wild-type PKR in patients with SCD may reduce hemoglobin polymerization and the sickling process by at least two mechanisms. Reducing the level of 2,3-DPG in RBCs would increase the oxygenation state of hemoglobin to reduce sickling, while increasing the levels of ATP may improve RBC hydration status which may also inhibit the sickling process.

Lower Risk MDS

MDS is a heterogeneous group of rare hematological malignancies characterized by dysfunctional hematopoiesis (or formation of blood cells), progressive cytopenia (or lower-than-normal number of blood cells) and an increased risk of progression to acute myeloid leukemia. The most common type of MDS is lower risk, or LR, MDS, but many existing therapies and therapies under development focus on high risk MDS. Among patients with LR MDS, which is less likely to progress to acute myeloid leukemia, the primary concern is symptomatic anemia. We estimate that the prevalence of LR MDS in the United States and EU5 is between 75,000 and 80,000 individuals. We believe that activation of wild-type PK in LR MDS patients may improve deficient PK activity in MDS erythrocytes. Current treatment options for LR MDS often require in-office visits and transfusions, and erythropoiesis stimulating agents and Reblozyl® (luspatercept-aamt) are the only approved therapies to treat

anemia in a subset of patients. Despite approved therapies in subsets of patients, LR MDS associated anemia remains a disease with a high unmet medical need.

Phenylketonuria

Phenylketonuria, or PKU, is a rare, genetic disease caused by deficiency of the PAH enzyme. Lack of PAH activity leads to the accumulation of phenylalanine and downstream neurocognitive deficits. Patients with PKU are therefore often advised to consume a highly restricted diet to in order to minimize phenylalanine intake, which can further reduce patient quality of life. We estimate that the prevalence of PKU in the United States and EU5 is between 35,000 and 40,000 individuals. To directly address the underlying cause of PKU, we are developing a PAH stabilizer with a goal of reducing phenylalanine levels.

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 November 2022, we received marketing authorization from the European Commission for PYRUKYND® for the treatment of PK deficiency in adult patients in the EU. In December 2022, we received marketing authorization in Great Britain for PYRUKYND® for the treatment of PK deficiency in adult patients under the European Commission Decision Reliance Procedure. In addition, we are currently evaluating PYRUKYND® in clinical trials for the treatment of thalassemia, SCD, and in pediatric patients with PK deficiency. 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 European Medicines Agency, or 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. We are currently providing access to PYRUKYND® free of charge for eligible patients in the EU and Great Britain through a global managed access program. 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 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 complete enrollment by mid-year 2023.
- 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 complete enrollment by mid-year 2023.
- 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 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 has been fully enrolled, and we expect to

announce the data from the phase 2 portion of this trial and decide whether we are initiating the phase 3 portion of this trial by mid-year 2023.

- 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 patients 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, and we expect to enroll at least half of the patients by year-end 2023.
- 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 Company, the National Institutes of Health, or NIH, is 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, and 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 the Company, UMC Utrecht, or UMC, is 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 and Other Programs

We are developing AG-946, a novel PK activator, for the potential treatment of LR MDS and hemolytic anemias. We are evaluating AG-946, in a phase 1 trial of AG-946 in healthy volunteers and in patients with SCD. We have presented data from the healthy volunteer cohort, and we have initiated the SCD patient cohort of this trial. We are evaluating AG-946 in a phase 2a study in adults with LR MDS, and we expect to complete enrollment by year-end 2023.

In addition to the aforementioned development programs, we are advancing our late-stage research program focused on a PAH stabilizer for the treatment of PKU, for which we expect to file an investigational new drug application by year-end 2023.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our product candidates and our core technologies, including novel biomarker and diagnostic discoveries, and other know-how, to operate without infringing on the proprietary rights of others and to prevent others from infringing on our proprietary or intellectual property rights. Our policy is to seek to protect our proprietary and intellectual property position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on confidential information, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position. We may also choose to rely on trade secrets to protect certain aspects of our business that are not suitable or appropriate for patent protection.

We file, or may collaborate with third parties to file, patent applications directed to our key products and product candidates, including PYRUKYND® and AG-946, in addition to related compounds and potential back-up compounds, in an effort to establish intellectual property positions to protect these new chemical entities as well as methods of using these compounds in the treatment of diseases, formulations, solid state forms, and manufacturing processes. We may also seek patent protection for certain biomarkers that may be useful in identifying the appropriate patient population for therapies with our product candidates.

PK activator program

The patent portfolio for our PK activator program contains issued patents and pending patent applications directed to compositions of matter for PYRUKYND®, as well as to related compounds, various solid state forms of PYRUKYND®, compositions of matter for additional PKR activators, such as AG-946, as well as methods of use for these novel compounds. As of February 1, 2023, we owned 11 issued U.S. patents and 190 issued foreign patents, and have pending patent applications

in the US and in various foreign jurisdictions. The patents that have issued or will issue for our PK activator program will have a statutory expiration date of at least 2030 to 2042. Patent term adjustments or patent term extensions could result in later expiration dates. In some cases, the term of a US patent can be shortened by the filing of a terminal disclaimer which operates to reduce the term of a patent to that of an earlier expiring patent. The foreign issued patents and pending patent applications are in a number of jurisdictions, including Argentina, Australia, Austria, Belgium, Brazil, Canada, China, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Lebanon, Lithuania, Mexico, the Netherlands, Norway, Poland, Portugal, Romania, Russia, Saudi Arabia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Taiwan, Turkey, and the United Kingdom. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the U.S. Patent and Trademark Office, or USPTO, can be significantly narrowed by the time they issue, if they issue at all. We expect this could be the case with respect to some of our pending patent applications referred to above.

Patent Term

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application, although term extensions may be available. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. The extension of the term of foreign patents varies, in accordance with local law. Although certain of the patents granted by the regulatory authorities of the EU may expire at specific dates, the terms of patents granted in certain European countries may extend beyond such EU patent expiration date if we were to obtain a supplementary protection certificate. In addition, because of the extensive time required for clinical development and regulatory review of a product candidate we may develop, it is possible that, before any of our product candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of any such patent.

In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each medicine and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

Additional Considerations

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our product, product candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, patent applications that we may file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, a third party can challenge the patentability of one or more of the claims of an issued patent in a post-grant proceeding before the USPTO or a foreign patent office such as the European Patent Office, which can result in the loss of certain claims or the loss of an entire patent. In addition, it is possible that a third party has filed a patent application in the United States, or abroad, that claims the same technology or chemical structures that are claimed in our own patent applications or patents. In such cases, we may have to participate in legal proceedings or enter into a licensing arrangement, which could result in substantial costs to us, even if the eventual outcome is favorable to us. In addition to patent protection, we also rely upon unpatented confidential information, including confidential technical information, know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, by using confidentiality agreements with our collaborators, third-party service providers, scientific advisors, employees and consultants, and by invention assignment agreements with our employees. We also have agreements requiring assignment of inventions with selected consultants, scientific advisors and collaborators. The confidentiality agreements are designed to protect our proprietary information and, in the case of agreements or clauses requiring invention assignment, to grant us ownership of technologies that are developed through a relationship with a third party.

With respect to our proprietary cellular metabolism technology platform, we consider confidential information and know-how related to our cellular metabolism technology platform to be our primary intellectual property in this space. Confidential information and know-how can be difficult to protect. In particular, we anticipate that with respect to this technology platform, at least some of the technical information and know-how will, over time, become known 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.

Competition

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, development experience and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies, and public and private research institutions. PYRUKYND® and any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

We compete in the areas of pharmaceutical, biotechnology and other related markets that address rare diseases, particularly hemolytic anemias and PKU. There are other companies working to develop therapies in the field of rare diseases, including divisions of large pharmaceutical companies and biotechnology companies of various sizes.

Our competitors include: Bristol-Myers Squibb Company, or BMS; BioMarin Pharmaceutical, Inc., or BioMarin; bluebird bio, Inc., or bluebird; Merck & Co., Inc., or Merck; Novartis International AG, or Novartis; Novo Nordisk A/S, or Novo; Pfizer, Inc., or Pfizer;; Rocket Pharma LTD, or Rocket Pharma; Vertex Pharmaceuticals Incorporated, or Vertex, Emmaus Life Sciences, or Emmaus, Fibrogen, Inc., or Fibrogen, Fulcrum Therapeutics, Inc., or Fulcrum, and Geron Corporation, or Geron.

The most common methods for treating patients with rare diseases include dietary restriction, dietary supplementation or replacement, treatment of symptoms and complications, gene therapy, blood transfusions, stem cell transplant and enzyme replacement therapies. There are a number of marketed therapies available for treating patients with hemolytic anemias and PKU. For example, recently approved treatments for thalassemia, SCD, LR MDS and PKU include Reblozyl® from Merck/BMS (formerly Acceleron/BMS); Revlimid® from BMS; Lentiglobin® from bluebird; Adakveo® from Novartis; Oxbryta® from Pfizer; Kuvan® and Palynziq® from BioMarin and Endari® from Emmaus. While our product and product candidates may compete with existing medicines and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our product or product candidates may not be competitive with them. In addition to currently marketed therapies, there are also a number of products that are either small molecules, biologics, enzyme replacement therapies or gene therapies in various stages of clinical development to treat hemolytic anemias and PKU. For example, Rocket Pharma is conducting a clinical trial of a gene therapy targeting PK deficiency, Novo is developing etavopivat (a PKR activator) for the treatment of hemolytic anemias, including thalassemia, SCD and MDS, Pfizer is developing inclacumab and GBT-601 for the treatment of SCD, Fibrogen is developing roxadustat for the treatment of anemia in MDS patients, Geron is developing imetelstat for the treatment of LR MDS, Vertex is developing a gene therapy targeting SCD, and Fulcrum is developing FTX-6058 in SCD, and a number of companies, including PTC Therapeutics, Inc., or PTC, Synlogic, Inc., or Synlogic, and Jnana Therapeutics, Inc., or Jnana, are developing therapies to treat PKU. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide competition for any of our product or product candidates for which we obtain market approval.

Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and globally marketing approved medicines than we do. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel, and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring or in-licensing technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of PYRUKYND® and any of our product candidates that we develop, if approved, are likely to be their efficacy, safety, convenience, price, the effectiveness of companion diagnostics in guiding the use of related therapeutics where appropriate, the level of generic competition and the availability of reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize medicines that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any medicines that we may develop. Our competitors also may obtain FDA or other regulatory approval for their medicines 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. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic or other branded medicines. There are many generic medicines currently on the market for the indications that we are pursuing, and additional medicines are expected to become available on a generic basis over the coming years. We expect that PYRUKYND® and any of our product candidates that may receive marketing approval in the future will be priced at a significant premium over competitive generic medicines.

Manufacturing and Supply Chain

PYRUKYND®, AG-946, and PAH are organic compounds of low molecular weight, generally called small molecules. They can be manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistry is amenable to scale-up and does not require unusual equipment in the manufacturing process. We expect to continue to develop drug candidates that can be produced cost-effectively at contract manufacturing facilities.

We do not own or operate, and currently have no plans to establish, any manufacturing or supply chain related facilities. We currently, and expect to continue to, rely on third parties for the manufacture and supply of our clinical and preclinical product candidates, as well as for commercial manufacture of PYRUKYND® and any product for which we may receive marketing approval in the future. We conduct extensive prequalification programs to ensure the compliance, quality and reliability of third-party manufacturing and supply operations.

To date, we have obtained materials for PYRUKYND® and AG-946 for our ongoing and planned clinical testing from third-party manufacturers. We have long-term commercial manufacture and supply agreements in place for PYRUKYND®, and we obtain our supplies from these manufacturers on a purchase order basis.

Due to the volatility of the supply networks globally, we have gained regulatory approval for redundant supply of raw materials and active pharmaceutical ingredient, or API, for PYRUKYND®, and have an ongoing program to ensure this risk mitigation remains effective, including establishing safety stocks. We do not currently have arrangements in place for redundant supply for drug product, but maintain a broad safety stock program. As we have done for PYRUKYND®, we intend to identify and qualify additional manufacturing and supply related services for our other product candidates prior to submission of an NDA to the FDA.

Government Regulation and Product Approvals

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the EU, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of biopharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Approval and Regulation of Drugs in the United States

In the United States, drug products are regulated under the Federal Food, Drug and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. A company, institution, or organization which takes responsibility for the initiation and management of a clinical development program for such products, and for their regulatory approval, is typically referred to as a sponsor.

A sponsor seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be approved by the FDA:

- preclinical testing including laboratory tests, animal studies and formulation studies which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;
- design of a clinical protocol and submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP;
- preparation and submission to the FDA of a NDA for a drug product which includes not only the results of the clinical trials, but also, detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labeling for one or more proposed indication(s);
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of FDA inspection of the manufacturing facility or facilities, including those of third parties, at which the product candidate or components thereof are manufactured to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP and the integrity of clinical data in support of the NDA;

- payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product; and
- compliance with any post-approval requirements, including the potential requirement to implement risk evaluation and mitigation strategies, or REMS, and the potential requirement to conduct any post-approval studies required by the FDA.

Preclinical Studies

Before a sponsor begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards, and the United States Department of Agriculture's Animal Welfare Act, if applicable. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND and are typically referred to as IND-enabling studies. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long-term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved NDA. In support of a request for an IND, sponsors must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements, including GCP requirements, of the FDA in order to use the study as support for an IND or application for marketing approval. The GCP requirements encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made based on evolving business objectives and/or competitive climate.

Reporting Clinical Trial Results

Under the Public Health Service Act, sponsors of certain clinical trials of certain FDA-regulated products, including prescription drugs and biologics, are required to register and disclose certain clinical trial information on a public registry (clinicaltrials.gov) maintained by the NIH. Information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. With the issuance of several notices of non-compliance since April 2021, the FDA and NIH have recently signaled the government's willingness to begin enforcing these requirements against non-compliant clinical trial sponsors. The failure to submit clinical trial information to clinicaltrials.gov is also a prohibited act under the FDCA with violations subject to potential civil monetary penalties of up to $10,000 for each day the violation continues. Violations may also result in injunctions and/or criminal prosecution or disqualification from federal grants.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

While there is no obligation to make investigational products available for expanded access, sponsors are required to make policies for evaluating and responding to requests for expanded access publicly available upon the earlier of initiation of a Phase 2 or Phase 3 clinical trial, or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, the Right to Try Act, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of a qualified investigator in accordance with GCP requirements which include, among other things, the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under written clinical trial protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in three sequential phases, but the phases may overlap or be combined.

Phase 1 clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy humans or in patients. During Phase 1 clinical trials, information about the investigational drug product's pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid Phase 2 clinical trials.

Phase 2 clinical trials are generally conducted to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications, and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials. Phase 2 clinical trials are well controlled, closely monitored and conducted in a limited patient population.

Phase 3 clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy, and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. The FDA may require more than one Phase 3 clinical trial to support approval of a product candidate. A well-controlled, statistically robust Phase 3 clinical trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug; such Phase 3 clinical trials are referred to as "pivotal." A Phase 2 clinical trial can be a "pivotal" trial if the design provides a well-controlled and reliable assessment of clinical benefit, particularly in an area of unmet medical need.

A company's designation of the phase of a trial is not necessarily indicative that the trial will be sufficient to satisfy the FDA requirements of that phase.

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These trials are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Progress reports detailing the results of clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

Review and Approval of an NDA

In order to obtain approval to market a drug product in the United States, a marketing application must be submitted to the FDA that provides sufficient data establishing the safety and efficacy of the proposed drug product for its intended indication. The application must include all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a product use, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the drug product to the satisfaction of the FDA.

The NDA is a vehicle through which sponsors formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2023 is approximately $3.25 million. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2023 is approximately $394,000 per product. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

Following submission of an NDA, the FDA conducts a preliminary review of the application generally within 60 calendar days of its receipt and must inform the sponsor at that time or before whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. Under the goals and policies agreed to by the FDA under the Prescription Drug User Fee Act, or PDUFA, applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which the FDA accepts the application for filing. The review process and the PDUFA goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the sponsor to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Under the FDA Reauthorization Act of 2017, the FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain applications, including applications for products in shortage or those for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require a sponsor to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. REMS could include medication guides, communication plans for health care professionals, and elements to assure safe use, including special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. To determine whether a REMS is needed, the FDA will consider the size of the population

likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events and whether the product is an NME.

The FDA may refer an application for a novel product which presents difficult questions of safety or efficacy to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations when making decisions.

Fast Track, Breakthrough Therapy, Priority Review and Regenerative Advanced Therapy Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as Fast Track designation, Breakthrough Therapy designation, priority review designation and regenerative advanced therapy designation.

- *Fast Track Designation*. The FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review process may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. However, the FDA's time period goal for reviewing a Fast Track application does not begin until the last section of the application is submitted. In addition, the Fast Track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.
- *Breakthrough Therapy Designation*. A product may be designated as a Breakthrough Therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. The FDA may take certain actions with respect to Breakthrough Therapies, including: holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.
- *Priority Review*. The FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for review of a marketing application from ten months to six months.
- *Regenerative Advanced Therapy Designation*. A product is eligible for regenerative advanced therapies designation if it is a regenerative medicine therapy that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

Accelerated Approval Pathway

Drug or biologic products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval. Accelerated approval means that a product candidate may be approved on the basis of adequate and well controlled clinical trials establishing that the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity and prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug or biologic product candidate receiving accelerated approval perform adequate and well controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials.

The FDA's Decision on an NDA

Based on its evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes

commercial marketing of the product with specific prescribing information for the approved indications. A complete response letter generally indicates that the review cycle is complete and outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. A sponsor has one year to respond to the deficiencies identified in the complete response letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a new product, it may limit the approved indications for use of the product. The FDA may also require contraindications, warnings or precautions be included in the product labeling, require post-approval trials, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms, including REMS,to help ensure that the benefits of the product outweigh the potential risks. The FDA may prevent or limit further marketing of a product based on the results of post-marketing trials or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Under the Ensuring Innovation Act, signed into law in 2021, the FDA must publish action packages summarizing its decisions to approve new drugs within 30 days of approval of such drugs.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA may have imposed as part of the approval process. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP and other regulatory requirements.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, with manufacturing processes, or failure to comply with regulatory requirements, may result in: revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information, although it may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information. In the United States, health care professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the

practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. In September 2021, the FDA published final regulations that describe the types of evidence that the agency will consider in determining the intended use of a drug or biologic.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the DOJ, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCSA, which regulate the distribution and tracing of prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCSA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical trials which must contain substantial evidence of the safety and efficacy of the proposed new product for the proposed use. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the sponsor for approval of the application "were not conducted by or for the sponsor and for which the sponsor has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the sponsor. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the 505(b)(2) sponsor can establish that reliance on the FDA's previous approval is scientifically appropriate, the sponsor may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) sponsor.

Generic Drugs and Regulatory Exclusivity

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. Such previously approved drugs are known as the reference listed drugs, or RLDs. Abbreviated new drug applications, or ANDAs, for generic drugs generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, the sponsor may rely on the preclinical and clinical testing previously conducted for the RLD.

Under the Hatch-Waxman Act, the FDA may not approve an ANDA or 505(b)(2) application until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity, or NCE. For the purposes of this provision an NCE is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, a generic or follow-on drug application may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the sponsor may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the sponsor and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as new indications, dosage forms, route of administration, combination of ingredients. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the

FDA from accepting ANDAs or 505(b)(2) NDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product; rather, this three-year exclusivity covers only the conditions of use associated with the new clinical investigations and, as a general matter, does not prohibit the FDA from approving follow-on applications for drugs containing the original active ingredient.

Upon submission of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the sponsor's product or an approved method of using the product. Upon approval of a new drug, each of the patents listed by the NDA sponsor is published in the FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the Orange Book. When an ANDA sponsor files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book. Specifically, the sponsor must certify: (i) the required patent information has not been filed, (ii) the listed patent has expired, (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration or (iv) the listed patent is invalid, unenforceable or will not be infringed by the new product. To the extent that the Section 505(b)(2) sponsor is relying on studies conducted for an already approved product, the sponsor is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA sponsor would.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the sponsor does not challenge the listed patents, the ANDA or 505(b)(2) NDA will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA sponsor or the 505(b)(2) sponsor has provided a Paragraph IV certification to the FDA, the sponsor must also send notice of the Paragraph IV certification to the NDA owner and patent holders once the ANDA or 505(b)(2) NDA has been accepted for filing by the FDA. The NDA owner and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) NDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA or 505(b)(2) sponsor.

Pediatric Studies

Under the Pediatric Research Equity Act of 2003, or PREA, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the sponsor plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The sponsor, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the sponsor may request an amendment to the plan at any time.

For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of a sponsor, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, the FDA will meet early in the development process to discuss pediatric study plans with sponsors, and the FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety (90) days after the FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the sponsor, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. A deferral may be granted for several reasons, including a finding that the product or therapeutic candidate is ready for approval for use in adults before pediatric trials are complete or that additional safety or effectiveness data needs to be collected before the pediatric trials begin. The law now requires the FDA to send a PREA Non-Compliance letter to sponsors who have failed to submit their pediatric assessments required under PREA, have failed to seek or obtain a deferral or deferral extension or have failed to request approval for a required pediatric formulation. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation, although FDA has recently taken steps to limit what it considers abuse of this statutory exemption in PREA by announcing that it does not intend to grant any additional orphan drug designations for rare pediatric subpopulations of what is otherwise a common disease. The FDA maintains a list of diseases that are exempt from the requirements of the PREA.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months to the term of any existing patent or regulatory exclusivity for drug products. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the

clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which a generic (ANDA or 505(b)(2) NDA) sponsor submitted a Paragraph IV certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by a proposed generic product.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must seek orphan drug designation before submitting an NDA for the candidate product. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation, or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same condition for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different conditions. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

Orphan drug exclusivity will also not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same condition is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand. This is the case despite an earlier court opinion holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

In September 2021, the Court of Appeals for the 11th Circuit held that, for the purpose of determining the scope of market exclusivity, the term "same disease or condition" in the statute means the designated "rare disease or condition" and could not be interpreted by the FDA to mean the "indication or use." Thus, the court concluded that orphan drug exclusivity applies to the entire designated disease or condition rather than the "indication or use." It is unclear how this court decision will be addressed by the FDA and Congress.

Patent Term Restoration and Extension

A patent claiming a new drug product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of when a clinical investigation involving human beings has begun and the submission date of an application for approval, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA.

Health Care Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state health care laws and regulations, include the following:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or

service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare and Medicaid;

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any health care benefit program or making false statements relating to health care matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;
- the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;
- the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the ACA, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, or HHS, information related to payments and other transfers of value made by that entity to physicians, other healthcare providers and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to health care items or services that are reimbursed by non-government third-party payors, including private insurers.

Further, 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 in addition to requiring manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. 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.

Violations of these laws are punishable by criminal and/or civil sanctions, including, in some instances, exclusion from participation in federal and state health care programs, such as Medicare and Medicaid.

Pharmaceutical Insurance Coverage and Health Care Reform

In the United States and other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated health care costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels for the product. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product

could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of health care costs also has become a priority of federal, state and foreign governments, and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs, biologics and other medical products, government control and other changes to the health care system in the United States.

In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Among the provisions of the ACA of importance to our potential product candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs, and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% (and 70% starting January 1, 2019) point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which will remain in effect through 2031. However, pursuant to the Coronavirus Aid, Relief and Economic Security Act and subsequent legislation, these Medicare reductions were reduced and suspended through the end of June 2022 with the full 2% cut resuming thereafter.

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, with enactment of the Tax Cuts and Jobs Act of 2017 on December 22, 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 of 2017, the remaining provisions of the ACA are invalid as well. On June 17, 2021, the Supreme Court dismissed this action after finding that the plaintiffs did not have standing

to challenge the ACA's minimum essential coverage provision at issue in the case. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

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

Pharmaceutical Prices

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. To date, there have been several recent U.S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and 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 drug products. Certain of these orders are reflected in recently promulgated regulations, including an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician-administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021, but such rule has been subject to a nationwide preliminary injunction. In December 2021, the CMS issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence-based care.

In November 2020, the HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule went into effect on January 1, 2023. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which has been delayed until January 1, 2026 by the Infrastructure Investment and Jobs Act. In addition, in response to an executive order from President Biden, the HHS recently released a plan to reduce pharmaceutical prices.

More recently, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Medicare Part D drugs in 2027, 15 Medicare Part B or Part D drugs in 2028, and 20 Medicare Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated "maximum fair price" under the law or for taking price increases that exceed inflation. The legislation also requires manufacturers to pay rebates for drugs in Medicare Part D whose price increases exceed inflation. 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. For example, 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 importation from Canada with the intent of developing SIPs for review and approval by the FDA. A number of states have also required drug manufacturers and other entities in the drug supply chain, including health carriers, pharmacy benefit managers and wholesale distributors, to disclose information about pricing of pharmaceuticals. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy, and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, a sponsor will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the EU generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application, or MAA, and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

Before the new Clinical Trial Regulation, (EU) No 536/2014, or the Clinical Trial Regulation came into application in January 2022, requirements for the conduct of clinical trials in the EU including GCP were set forth in the Clinical Trials Directive 2001/20/EC, or the Clinical Trials Directive, and the GCP Directive 2005/28/EC, or the GCP Directive. Under this system, a sponsor must obtain prior approval from the competent national authority of the EU Member States in which the clinical trial is to be conducted. Furthermore, the sponsor may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by the Clinical Trials Directive and the GCP Directive, where relevant the implementing national provisions of the individual EU Member States and further detailed in applicable guidance documents.

In April 2014, the Clinical Trial Regulation was adopted. The Clinical Trial Regulation aims to simplify and streamline the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the EU Portal and Database; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted, or Concerned Member States. Part II is assessed separately by each Concerned Member State. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the Concerned Member State. However, overall related timelines will be defined by the Clinical Trial Regulation.

The Clinical Trial Regulation came into application on January 31, 2022 and is directly applicable in all the EU Member States, repealing the previous Clinical Trials Directive. Conduct of all clinical trials performed in the EU were bound by previously applicable provisions until the new Clinical Trial Regulation became applicable. If a clinical trial continues for more than three years from the day on which the Clinical Trial Regulation became applicable, the Clinical Trial Regulation will begin to apply to the clinical trial as of the time of its effectiveness.

Parties conducting certain clinical trials must, as in the United States, post clinical trial information in the EU at the EudraCT website: https://eudract.ema.europa.eu.

PRIME Designation in the EU

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The priority medicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises may qualify for

earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated agency contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies are appointed early in the PRIME scheme facilitating increased understanding of the product at EMA's Committee level.

Marketing Authorization

To obtain a marketing authorization for a product under EU regulatory systems, a sponsor must submit an MAA either under a centralized procedure administered by the EMA, or one of the procedures administered by competent authorities in the EU Member States, decentralized procedure; national procedure; or mutual recognition procedure.

The centralized procedure provides for the grant of a single marketing authorization by the EMA that is valid in all EU Member States, as well as Iceland, Liechtenstein and Norway. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products, and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. The centralized procedure may at the request of the sponsor also be used in certain other cases. The centralized procedure is optional for products that represent a significant therapeutic, scientific or technical innovation, or whose authorization would be in the interest of public health.

Under the centralized procedure, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the sponsor in response to questions of the CHMP. Accelerated assessment might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and from the viewpoint of therapeutic innovation. The timeframe for the evaluation of an MAA under the accelerated assessment procedure is 150 days, excluding stop clocks.

There are also two other possible routes to authorize medicinal products in several EU countries, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:

- *Decentralized procedure*. Using the decentralized procedure, a sponsor may apply for simultaneous authorization in more than one EU country of medicinal products that have not yet been authorized in any EU country and that do not fall within the mandatory scope of the centralized procedure. The sponsor may choose a member state as the reference member state to lead the scientific evaluation of the application.
- *Mutual recognition procedure*. In the mutual recognition procedure, a medicine is first authorized in one EU Member State (which acts as the reference member state), in accordance with the national procedures of that country. Following this, further marketing authorizations can be progressively sought from other EU countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization produced by the reference member state.

Under the above-described procedures, before granting the marketing authorization, the EMA or the competent authorities of the Member States of the European Economic Area, or EEA, make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Conditional Approval

The European Commission may also grant a so-called "conditional marketing authorization" prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations may be granted for product candidates (including medicines designated as orphan medicinal products), if (i) the product candidate is intended for the treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, (ii) the risk-benefit balance of the product candidate is positive; (iii) it is likely that the sponsor will be in a position to provide the required comprehensive clinical trial data; (iv) the product fulfills an unmet medical need; and (v) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new clinical studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization, but applicants can also request the EMA to conduct an accelerated assessment, for instance in cases of unmet medical needs.

Regulatory Data Protection in the EU

In the EU, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance with the centralized authorization procedure. Data exclusivity prevents sponsors for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic MAA can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the EU market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be an NCE so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical, preclinical and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU Member States may decide, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in case of centralized procedure) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid (the so-called sunset clause).

Pediatric Studies and Exclusivity

Prior to obtaining a marketing authorization in the EU, sponsors must demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are laid down in Regulation (EC) No 1901/2006, the so-called Pediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Pediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the adult population. Before an MAA can be filed or an existing marketing authorization can be amended, the EMA requests that companies comply with the agreed studies and measures listed in each relevant PIP. If a sponsor obtains a marketing authorization in all EU Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate, or SPC, or alternatively a one year extension of the regulatory market exclusivity from ten to eleven years, as selected by the marketing authorization holder.

Orphan Drug Designation and Exclusivity

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a drug can be designated as an orphan drug by the European Commission if its sponsor can establish that the product is intended for the diagnosis, prevention or treatment of: (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made; or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the sponsor must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to 10 years of market exclusivity in all EU Member States and a range of other benefits during the development and regulatory review process, including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries, and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar

medicinal product with the same orphan indication during the 10-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Patent Term Extensions

The EU also provides for patent term extension through SPCs. The rules and requirements for obtaining an SPC are similar to those in the United States. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of fifteen years of marketing exclusivity for a drug. In certain circumstances, these periods may be extended for six additional months if pediatric exclusivity is obtained. Although SPCs are available throughout the EU, sponsors must apply on a country by country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the EU.

Regulatory Requirements after a Marketing Authorization has been Obtained

When an authorization for a medicinal product in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

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

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR 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 the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance. In July 2020, the Court of Justice of the European Union, or the CJEU, invalidated the EU-U.S. Privacy Shield framework, one of the mechanisms used to legitimize the transfer of personal data from the EEA to the United States. The CJEU decision also drew into question the long-term viability of an alternative means of data transfer, the standard contractual clauses, for transfers of personal data from the EEA to the United States.

Additionally, in October 2022, President Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-U.S. Privacy Shield. The EC initiated the process to adopt an adequacy decision for the EU-U.S. Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the EU.

Following the withdrawal of the U.K. from the EU, the U.K. Data Protection Act 2018 applies to the processing of personal data that takes place in the U.K. and includes parallel obligations to those set forth by GDPR, including in relation to data transfers.

Brexit and the Regulatory Framework in the United Kingdom

The U.K.'s withdrawal from the EU took place on January 31, 2020. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law whereas Northern Ireland continues to be subject to EU rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law, the body of EU law instruments governing medicinal products that pre-existed prior to the U.K.'s withdrawal from the EU. Since a significant proportion of the regulatory framework for pharmaceutical products in the U.K. 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, Brexit may have a material impact upon the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the U.K. For example, the U.K. is no longer covered by the centralized procedures for obtaining EU-wide marketing authorization from the EMA, and a separate marketing authorization will be required to market any product candidates in the U.K. Until December 31, 2023, it is possible for the MHRA to rely on a decision taken by the European Commission/EMA's CHMP on the approval of a new marketing authorization via the centralized procedure, which is the Reliance Procedure.

Pricing Decisions for Approved Products

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the EU provides options for its Member States to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals, and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and there negotiations may continue after reimbursement has been obtained. Reference pricing used by various Member States, and parallel trade (i.e., arbitrage between low-priced and high-priced Member States), can further reduce prices. There can be no assurance that any country with price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Segment Reporting and Geographical Information

We are engaged solely in the discovery and development of medicines in the field of cellular metabolism. Accordingly, we have determined that we operate in one operating segment.

Employees and Human Capital

As of December 31, 2022, we had 389 full-time employees and 4 part-time employees, all based in the United States and of which 101 held Ph.D., Pharm.D. or M.D. degrees. None of our employees are represented by a labor union or covered under a collective bargaining agreement. We also retain independent contractors to support the goals of our organization. We prioritize our employee experience and we are proud of our strong employee and contractor relations.

We understand that attracting, retaining, engaging and supporting our talented team and maintaining a diverse and inclusive organization is critical to our success and our ability to increase the value we can provide for patients, shareholders and all stakeholders.

We strive to cultivate a positive, respectful and fair work environment guided by the following three pillars:

- *Flexibility*: We provide flexible work arrangements which result in happier, more engaged and more productive employees. We encourage a culture that promotes different perspectives, different work styles, health and wellness, care of families and productivity.
- *Psychological safety*: We aim to ensure our teams experience psychological safety – the belief that risk-taking and failure will not be punished, which leads to higher performing teams, more creativity, candor and better results.

- *Deliberate development*: We emphasize providing ongoing opportunities for employees to grow professionally, whether through bringing in external speakers, offering preceptorships in different departments, and providing tuition reimbursement and leadership skills training.

To incentivize and reward strong performance, we have established a competitive and balanced compensation and benefits package, including short-term and long-term incentives, discretionary paid time off policy, generous parental and family leave plans and premium medical benefits.

We are committed to fostering a welcoming and diverse workplace in which individuals from a variety of backgrounds can thrive. Our diversity and inclusion program focuses on valuing three types of differences:

- Representative differences (demographic diversity, such as gender, race, ethnicity, sexual orientation)
- Experiential differences (identities based on life experiences that may change over time)
- Cognitive differences (unique ways of understanding and interpreting the world)

We are a majority female organization and we maintain significant representation at all levels, including the Board of Directors. As of December 31, 2022, 59% of our workforce were women. Racial and ethnic diversity continues to be an area of focus for improvement at the Company. As of December 31, 2022, 31% of our workforce were ethnically diverse and 38% of all new hires that joined the Company in 2022 were ethnically diverse. We have an active cross-functional diversity council that furthers our commitment to building a diverse and inclusive organization by:

- Representing and reflecting the different voices in the Agios community
- Furthering the work of diversity, equity and inclusion at Agios and in our communities
- Working in partnership with our leadership, human resources and employee resource groups to share, drive and lead our diversity, equity and inclusion efforts

We recognize that there is still important progress to be made, particularly as it relates to Black and Latino representation at our company, and this remains an area of continued emphasis for us.

We regularly evaluate the effectiveness of our human capital management practices through employee surveys and fostering a culture of ongoing feedback and two-way dialogue. In addition, we track important human capital metrics such as turnover rate. Voluntary and involuntary turnover rates across all levels (executives/ senior managers, mid-level managers and professionals) are in alignment with, or lower than, the industry average.

The COVID-19 pandemic evolved throughout 2022 and we continued to demonstrate our commitment to the health and well-being of our employees, our patients and our community. We continue to monitor local and national public health data to determine if adjustment to our work practices is needed. We have maintained a mandatory vaccination policy for all employees, regardless of their role or work locations, subject to limited exceptions. Thoughtful management of our COVID-19 response continues to be a priority for our leadership team.

We have maintained our "Future of Work" policy providing employees whose roles do not require an onsite or in field presence with an opportunity to choose the right working arrangement for them: whether remote; hybrid with time split between home or the office; or primarily onsite in our Cambridge office, and we continue to evaluate how we can enhance these arrangements for an optimal employee experience. The opportunity to work remotely has enabled us to hire a more diverse team including individuals from different locations and backgrounds and with a variety of responsibilities in their personal lives. In 2022, 67% of our new hires chose to work remotely.

We believe our ability to embrace change and our long-standing culture and values around flexibility and connection have helped us deliver for patients.

Our Corporate Information

Our executive offices are located at 88 Sidney Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 649-8600. Our website address is www.agios.com. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Form 10-K.

Available Information

Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge on our website located at www.agios.com as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission, or SEC. These reports are also available at the SEC's website at www.sec.gov.

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation & People Committee, and Nominating and Corporate Governance Committee are posted on our website, www.agios.com, under the heading "Corporate Governance" and are available in print to any person who requests copies by contacting us by calling (617) 649-8600 or by writing to Agios Pharmaceuticals, Inc., 88 Sidney Street, Cambridge, Massachusetts 02139.

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K 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 1 of this Annual Report on Form 10-K 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. In November 2022, we received marketing authorization from the European Commission for PYRUKYND® for the treatment of PK deficiency in adult patients in the EU, and in December 2022 we received marketing authorization in Great Britain for PYRUKYND® for the treatment of PK deficiency in adult patients under the European Commission Decision Reliance Procedure. 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 rare disease portfolio that has received marketing approval. As of the date of this Annual Report on Form 10-K, we are in the process of commercially launching PYRUKYND® in the United States. 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 adults with PK deficiency in the approved jurisdictions;
- 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 obtain marketing approval of PYRUKYND® in other indications;
- new significant safety, manufacturing and/or quality 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®, upon approval, for use in indications other than PK deficiency. 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®. While we obtained marketing approval of PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States and marketing authorization of PYRUKYND® for the treatment of adults with PK deficiency in the European Union and Great Britain, we cannot be certain that we will obtain marketing approval of PYRUKYND® in indications other than PK deficiency.

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 rare disease 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 in the future affect our ability to initiate or continue our planned, ongoing and future preclinical studies, 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 preclinical studies and 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 was and may again in the future 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 in the future 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 in the future, necessitate remote data verification. In addition, limitations on 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 in the future 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 in the future 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 rare disease 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; Novo Nordisk is developing molecules for the treatment of beta thalassemia and SCD; 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 LR MDS; Roivant Sciences is developing RVT-2001 (licensed from Eisai Co., Ltd.) for the treatment of transfusion-dependent anemia in patients with LR MDS; and PTC Therapeutics, Inc., or PTC, Synlogic, Inc., or Synlogic, and Jnana Therapeutics, Inc., or Jnana, are developing therapies to treat PKU. 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 and marketing authorization of PYRUKYND® for the treatment of adults with PK deficiency in the European Union and Great Britain, we cannot be certain that we will obtain marketing approval of PYRUKYND® in other indications. 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. We have decided 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, our phase 2a trial in LR MDS and our IND-enabling studies for our PAH stabilizer for the treatment of PKU. 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 and are currently providing access to PYRUKYND® free of charge for eligible patients in the EU and Great Britain through a global managed access program, we may need to further build our sales and marketing infrastructure, either directly or with a third-party partner, 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 LR 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 Pfizer are each marketing therapies to treat SCD, Rocket Pharma is conducting a clinical trial of a gene therapy targeting PK deficiency, Fulcrum Therapeutics, Inc. is developing a potential treatment for SCD, 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 rare diseases. 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 rare diseases. 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 rare diseases 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, Novo Nordisk, PTC, 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 globally 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 or in-licensing 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 sponsor 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 sponsor and for which the sponsor 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 sponsor 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 sponsor 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.

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

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

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

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

In 2018, California passed into law the California Consumer Privacy Act, or CCPA, which took effect on January 1, 2020 and imposed many requirements on businesses that process the personal information of California residents. Many of the CCPA's requirements are similar to those found in the General Data Protection Regulation, or GDPR, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt-out of "sales" of their personal information. The CCPA contains significant penalties for companies that violate its requirements. In November 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR-like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The provisions in the CPRA may apply to some of our business activities. In addition, other states, including Virginia, Colorado, Utah, and Connecticut already have passed state privacy laws. Virginia's privacy law also went into effect on January 1, 2023, and the laws in the other three states will go into effect later in the year. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. These laws may impact our

business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products.

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

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

Additionally, in October 2022, President Joe Biden signed an executive order to implement the EU-U.S. Data Privacy Framework, which would serve as a replacement to the EU-U.S. Privacy Shield. The European Commission initiated the process to adopt an adequacy decision for the EU-U.S. Data Privacy Framework in December 2022. It is unclear if and when the framework will be finalized and whether it will be challenged in court. The uncertainty around this issue may further impact our business operations in the EU.

Following Brexit, the UK Data Protection Act 2018 applies to the processing of personal data that takes place in the United Kingdom and includes parallel obligations to those set forth by GDPR. In relation to data transfers, both the United Kingdom and the EU have determined, through separate "adequacy" decisions, that data transfers between the two jurisdictions are in compliance with the UK Data Protection Act and the GDPR, respectively. Any changes or updates to these adequacy decisions have the potential to impact our business.

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

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

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 rare diseases. The success of the rare disease business is subject to various risks and uncertainties, including the possibility that we may not be able to successfully commercialize PYRUKYND®, the possibility of

adverse clinical and other developments in respect of PYRUKYND® or our other product candidates of the rare disease business, and unanticipated changes in applicable laws and regulations that may adversely affect the rare disease 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 rare diseases. As a result, we may be more susceptible to changing market conditions, including fluctuations and risks particular to the markets for patients with rare diseases, 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, 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 significant 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 significant 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 adults with PK deficiency in the approved jurisdictions;
- 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 twelve months ended December 31, 2022 was $231.8 million, our net income for the twelve months ended December 31, 2021 was $1.6 billion, and our net loss for the twelve months ended December 31, 2020 was $327.4 million. The net income for the twelve months ended December 31, 2021 was due to the sale of our oncology business to Servier on March 31, 2021. As of December 31, 2022, we had an accumulated deficit of $470.6 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®. Following receipt of marketing approval in February 2022, we have begun to commercialize PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States, and we only recently obtained marketing authorization of PYRUKYND® for the treatment of adults with PK deficiency in the European Union and Great Britain and are currently providing access to PYRUKYND® free of charge for eligible patients in the EU and Great Britain through a global managed access program. 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 nor have we obtained marketing approval for any of our other product candidates, all of which are in preclinical or clinical development stages.

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 approved indications in approved jurisdictions;
- 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 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. 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®, which we sold 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, which are outside of our control, 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, we cannot predict 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, economic relief legislation was enacted in 2020 and 2021. Such legislation contains numerous tax provisions. In addition, the Inflation Reduction Act, or IRA, was signed into law in August 2022. The IRA introduced new tax provisions, including a 1% excise tax imposed on certain stock repurchases by publicly traded corporations. The 1% excise tax generally applies to any acquisition by the publicly traded corporation (or certain of its affiliates) of stock of the publicly traded corporation in exchange for money or other property (other than stock of the corporation itself), subject to a de minimis exception. Thus, the excise tax could apply to certain transactions that are not traditional stock repurchases. Regulatory guidance under the IRA, the Tax Act, and such additional legislation is and continues to be forthcoming, and such guidance could ultimately increase or lessen impact of these laws on our business and financial condition. In addition, it is uncertain if and to what extent various states will conform to the IRA, the Tax Act, and additional tax legislation.

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 or supply chain related 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 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 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, the emergence of another 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 preclinical development, clinical development, marketing approval or our commercialization efforts. Due to the volatility of the supply networks globally, we have obtained regulatory approval for redundant supply of raw materials and API for PYRUKYND®, and have an ongoing program to monitor supply, including establishing safety stocks. While we maintain a broad safety stock of drug product, 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.

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. 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. Although we have received marketing authorization for PYRUKYND® for the treatment of adults with PK deficiency in the European Union and Great Britain, we may not be able to file for additional marketing approvals and may not receive necessary approvals to commercialize our medicines in any other foreign 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. 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 on the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom remains unclear. As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or the MHRA, became responsible for supervising medicines and medical devices in Great Britain, comprising England, Scotland and Wales under domestic law, whereas Northern Ireland will

continue to be subject to European Union rules under the Northern Ireland Protocol. The MHRA will rely on the Human Medicines Regulations 2012 (SI 2012/1916) (as amended), or the HMR, as the basis for regulating medicines. The HMR has incorporated into the domestic law the body of European Union law instruments governing medicinal products that pre-existed Brexit. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may prevent us from commercializing any product candidates in the United Kingdom and/or the EU and may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom, 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 a sponsor 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.

We have built our commercial infrastructure to support the commercial launch of PYRUKYND® in adult PK deficiency in the United States. We are providing access to PYRUKYND® free of charge for eligible patients in the EU and Great Britain through a global managed access program. 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, and/or the sustainability of those prices.

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 rule went into effect on January 1, 2023. 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, on August 16, 2022, the Inflation Reduction Act of 2022, or IRA, was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years.

Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single-source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high-cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Medicare Part D drugs in 2027, 15 Medicare Part B or Part D drugs in 2028, and 20 Medicare Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products are the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on our drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years.

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.

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

In December 2019, former President Trump signed legislation intended to facilitate the development of generic and biosimilar products. The bill, previously known as the CREATES Act, authorizes sponsors of ANDAs and 505(b)(2) applications to file lawsuits against companies holding NDAs that decline to provide sufficient quantities of an approved reference drug on commercially reasonable, market-based terms. Drug products on FDA's drug shortage list are exempt from these new provisions unless the product has been on the list for more than six continuous months or the FDA determines that the supply of the product will help alleviate or prevent a shortage. For the purposes of the statute, the term "commercially reasonable, market-based terms" is defined as (1) the nondiscriminatory price at or below the most recent wholesale acquisition cost for the product, (2) a delivery schedule that meets the statutorily defined timetable, and (3) no additional conditions on the sale.

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

Additionally, the statutory provisions authorize a federal court to award the product developer an amount "sufficient to deter" the NDA holder from refusing to provide sufficient product quantities on commercially reasonable, market-based terms if the court finds, by a preponderance of the evidence, that the NDA holder did not have a legitimate business justification to delay providing the product or failed to comply with the court's order.

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

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 approximately 45 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 rare disease business following the sale of our oncology business to Servier;
- the evolution of our research organization;
- the impact of any repurchases by us of shares of common stock from our stockholders;

- announcements by us or our competitors of significant acquisitions, in-licensing arrangements, 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 December 31, 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, 2022, and determined that we did not have a qualified ownership change since our last review as of December 31, 2021. 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, 2022, 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, if any, 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 1B. Unresolved Staff Comments

None.

Item 2. Properties

We currently lease approximately 146,000 square feet at 88 Sidney Street, 43,000 square feet at 64 Sidney Street, and 13,000 square feet at 38 Sidney Street, Cambridge, Massachusetts. All leases, as amended, expire on February 29, 2028. At the end of the initial lease period, we have the option to extend the leases at all facilities for two consecutive five year periods at the fair market rent at the time of the extension. 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 believe our existing facilities are adequate for our current needs and that additional space will be available in the future on commercially reasonable terms as needed.

Item 3. Legal Proceedings

As of December 31, 2022, we were not a party to any material legal or arbitration proceedings. No governmental proceedings are pending or, to our knowledge, contemplated against us. We are not a party to any material proceedings in which any director, member of senior management or affiliate of ours is either a party adverse to us or our subsidiaries or has a material interest adverse to us or our subsidiaries.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock has been publicly traded on the Nasdaq Global Select Market under the symbol "AGIO" since July 24, 2013. Prior to that time, there was no public market for our common stock.

Holders

As of February 17, 2023, there were approximately 9 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Dividends

We have not declared or paid any cash dividends on our capital stock since our inception. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends to holders of common stock in the foreseeable future.

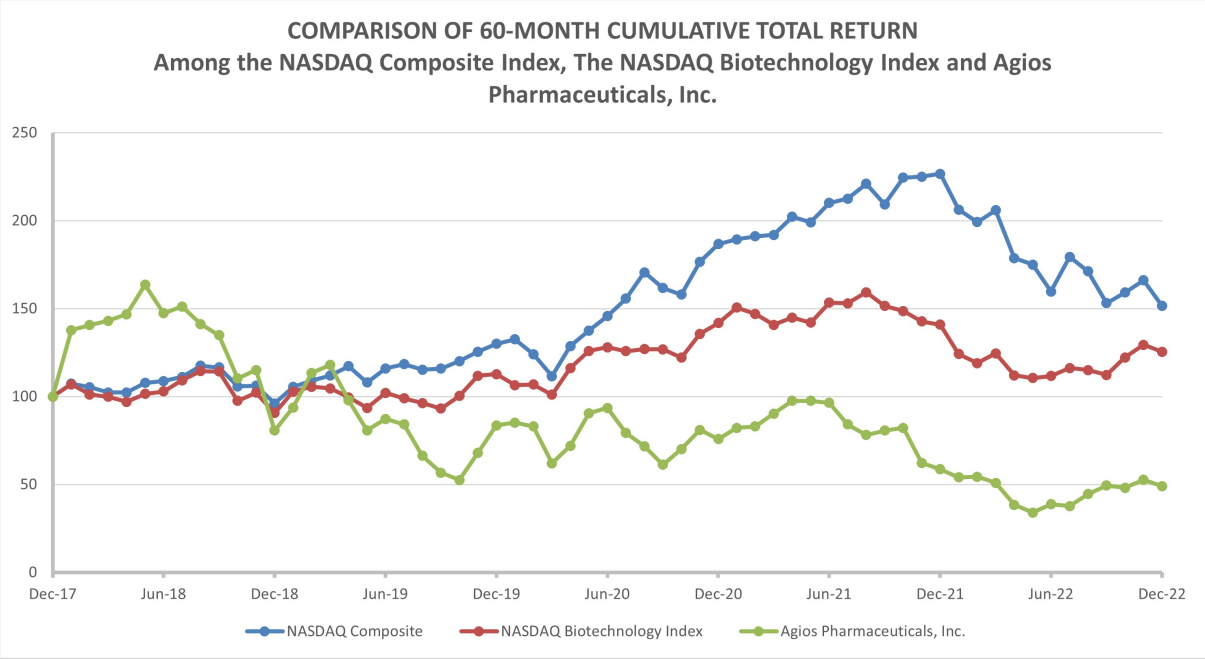
Securities Authorized for Issuance under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Item 12, *Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters*, of this Annual Report on Form 10-K.

Performance Graph

The following performance graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the Securities and Exchange Commission, or SEC, for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, nor shall such information be incorporated by reference into any future filing under the Exchange Act or the Securities Act of 1933, as amended, or the Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

The following graph compares the performance of our common stock to the NASDAQ Composite Index and the NASDAQ Biotechnology Index from December 31, 2017 through December 31, 2022. The comparison assumes $100 was invested after the market closed on December 31, 2017 in our common stock and in each of the foregoing indices, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.



Recent Sales of Unregistered Securities

None.

Purchases of Equity Securities by the Issuer or Affiliated Purchasers

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 December 31, 2022, we have not repurchased any shares under the Rule 10b-18 repurchase plan. In total, as of December 31, 2022, we repurchased 16.2 million shares of common stock for $802.5 million, or $49.49 per share, under the Repurchase Program.

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

Item 6. Reserved.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes and other financial information included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review "Item 1A, Risk Factors" of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

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 diseases. 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 rare diseases.

The lead product candidate in our portfolio, PYRUKYND® (mitapivat), is an activator of both wild-type and mutant pyruvate kinase, or PK, enzymes for the potential treatment of hemolytic anemias. In February 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 November 2022, we received marketing authorization from the European Commission for PYRUKYND® for the treatment of PK deficiency in adult patients in the European Union, or EU. In December 2022, we received marketing authorization in Great Britain for PYRUKYND® for the treatment of PK deficiency in adult patients under the European Commission Decision Reliance Procedure. 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, or LR MDS, and hemolytic anemias.

In addition to the aforementioned clinical development programs, we continue to invest in our late-stage research program focused on advancing a phenylalanine hydroxylase, or PAH, stabilizer for the treatment of phenylketonuria, or PKU.

Sale of Oncology Business to Servier Pharmaceuticals, LLC (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. The milestone payment for approval of vorasidenib and royalty payments related to vorasidenib and TIBSOVO® represent contingent consideration. Servier also acquired our co-commercialization rights for BMS'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.

The oncology business met the criteria within Accounting Standards Codification 205-20 to be reported as discontinued operations because the transaction was a strategic shift in business that had a major effect on our operations and financial results. Therefore, we have reported the historical results of the oncology business including the results of operations and cash flows as discontinued operations, and related assets and liabilities were retrospectively reclassified as assets and liabilities of discontinued operations for all periods presented herein. Unless otherwise noted, applicable amounts in the prior year have been recast to conform to this discontinued operations presentation. Refer to Note 15, *Discontinued Operations* of our consolidated financial statements included in this Annual Report on Form 10-K for additional information. A more complete description of our business prior to the consummation of the transaction is included in Item 1. "Business", in Part I of the Annual Report on Form 10-K for the year ended December 31, 2020 that was previously filed with the Securities and Exchange Commission, or SEC, on February 25, 2021.

Sale of Contingent Payments

The consideration for the sale of our oncology business to Servier includes a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity, referred to as contingent payments. We recognize the contingent payments in the royalty income from gain on sale of oncology business line item in our consolidated statement of operations in the period when realizable. On October 27, 2022, we sold our rights to future contingent payments to entities affiliated with Sagard Healthcare Partners, or Sagard, and recognized income of $127.9 million within the gain on sale of contingent payments line item in our consolidated statements of operations for the year ended December 31, 2022. 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 this 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 December 31, 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 contingent payments to Sagard, proceeds from the sale of contingent payments 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.

Additionally, since inception, we have incurred significant operating losses. Our net loss for the year ended December 31, 2022 was $231.8 million, our net income for the year ended December 31, 2021 was $1.6 billion and our net loss for the year ended December 31, 2020 was $327.4 million. As of December 31, 2022, we had an accumulated deficit of $470.6 million. The net income we generated in the year ended December 31, 2021 was 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 consolidated financial statements in this Form 10-K.

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 twelve months ended December 31, 2022 were expensed prior to February 17, 2022, and, therefore, are not included in costs of sales during the twelve months ended December 31, 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 rare disease 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 November 2022, we received marketing authorization from the European Commission for PYRUKYND® for the treatment of PK deficiency in adult patients in the EU. In December 2022, we received marketing authorization in Great Britain for PYRUKYND® for the treatment of PK deficiency in adult patients under the European Commission Decision Reliance Procedure. In addition, we are currently evaluating PYRUKYND® in clinical trials for the treatment of thalassemia, SCD, and in pediatric patients with PK deficiency. 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 European Medicines Agency, or 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. We are currently providing access to PYRUKYND® free of charge for eligible patients in the EU and Great Britain through a global managed access program. 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 complete enrollment by mid-year 2023.
- 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 complete enrollment by mid-year 2023.
- 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 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 has been fully enrolled, and we expect to announce the data from the phase 2 portion of this trial and decide whether we are initiating the phase 3 portion of this trial by mid-year 2023.
- 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 patients 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, and we expect to enroll at least half of the patients by year-end 2023.

- 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 Company, the National Institutes of Health, or NIH, is 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, and 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 the Company, UMC Utrecht, or UMC, is 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 and Other Programs

We are developing AG-946, a novel PK activator, for the potential treatment of LR MDS and hemolytic anemias. We are evaluating AG-946, in a phase 1 trial of AG-946 in healthy volunteers and in patients with SCD. We have presented data from 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 LR MDS in the third quarter of 2022, and we expect to complete enrollment by year-end 2023.

In addition to the aforementioned development programs, we are advancing our late-stage research program focused on a PAH stabilizer for the treatment of PKU, for which we expect to file an IND by year-end 2023.

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, information technology 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 rare disease portfolio, including the ongoing 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 Policies and Significant Judgments and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which we have prepared in accordance with accounting principles generally accepted in the United States. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported amounts of revenue and expenses during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements included in this Annual Report on Form 10-K, we believe that the following accounting policies are the most critical in fully understanding and evaluating our financial condition and results of operations and are policies that require a significant level of judgment and estimates.

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 our Customers, who 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.

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses. This process involves reviewing quotations and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. Certain service providers invoice us in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees

paid to: (i) CROs and other third parties in connection with clinical studies and preclinical development activities; (ii) investigative sites in connection with clinical studies; and (iii) third parties related to product manufacturing, development and distribution of clinical supplies.

We base our expenses related to CROs on our estimates of the services received and efforts expended pursuant to quotes and contracts with CROs that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in us reporting amounts that are too high or too low in any particular period.

Stock-based compensation

We account for stock-based compensation awards in accordance with ASC 718, *Compensation –Stock Compensation*. For stock-based awards granted to employees, non-employees and members of the board of directors for their services and for participation in our employee stock purchase plan, we estimate the grant date fair value of each option award using the Black-Scholes option-pricing model. The use of the Black-Scholes option-pricing model requires us to make assumptions with respect to the expected term of the option, the expected volatility of the common stock consistent with the expected life of the option, risk-free interest rates and expected dividend yields of the common stock.

Expected term. We use the "simplified method" as prescribed by the SEC Staff Accounting Bulletin No. 107, *Share Based Payments*, to estimate the expected term of stock option grants. Under this approach, the weighted-average expected life is presumed to be the average of the contractual term of ten years and the weighted-average vesting term of the stock options, taking into consideration multiple vesting tranches. We utilize this method due to lack of historical data and the plain-vanilla nature of our share-based awards.

Volatility. The expected volatility has been determined using Agios' historical volatilities for a period equal to the expected term of the option grant.

Risk-free rate. The risk-free rate is based on the yield curve of U.S. Treasury securities with periods commensurate with the expected term of the options being valued.

Dividends. We have never paid, and do not anticipate paying, any cash dividends in the foreseeable future, and, therefore, use an expected dividend yield of zero in the option-pricing model.

Forfeitures. We account for forfeitures as they occur and, therefore, do not estimate forfeitures.

For awards subject to service-based vesting conditions, we recognize stock-based compensation expense equal to the grant date fair value of stock options on a straight-line basis over the requisite service period. For awards subject to both performance and service-based vesting conditions, we recognize stock-based compensation expense over the remaining service period if the performance condition is considered probable of achievement using management's best estimates.

Discontinued Operations

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

Due to the sale of our oncology business during the first quarter of 2021, in accordance with ASC 205, we have classified the results of the oncology business as discontinued operations in our consolidated statements of operations and cash flows for all periods presented, and refer to Note 15, *Discontinued Operations* of our consolidated financial statements included in this

Annual Report on Form 10-K for additional information. All assets and liabilities associated with our oncology business were therefore classified as assets and liabilities of discontinued operations in our consolidated balance sheets for the periods presented. All amounts included in the notes to the consolidated financial statements relate to continuing operations unless otherwise noted.

Results of Operations

Certain prior-year amounts have been reclassified to conform with current presentation.

Comparison of years ended December 31, 2022, 2021 and 2020

Revenues

(In thousands)	2022	2021	2020
Revenues:			
Product revenue, net	$ 11,740	$ —	$ —
Milestone revenue	2,500	—	—
Total revenue	$ 14,240	$ —	$ —

Total Revenue – 2022 vs. 2021 – The increase in total revenue of $14.2 million in 2022 compared to 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)	2022	2021	2020
Operating expenses			
Cost of sales	$ 1,704	$ —	$ —
Research and development	279,910	256,973	220,811
Selling, general and administrative	121,673	121,445	115,105
Total Operating Expenses	$ 403,287	$ 378,418	$ 335,916

Total Operating Expenses – 2022 vs. 2021 – The increase in total operating expenses of $24.9 million in 2022 compared to 2021 was primarily due to an increase of $22.9 million in research and development expenses, which is described below under Research and Development Expenses.

Total Operating Expenses – 2021 vs 2020 – The increase in total operating expenses of $42.5 million in 2021 compared to 2020 was primarily due to an increase of $36.2 million in research and development expenses, which is described below under Research and Development Expenses, and an increase of $6.3 million in selling, general and administrative expense due to higher personnel costs related to additional hiring for our sales workforce and commercial launch preparation activities in anticipation of the FDA approval of PYRUKYND®. Included in selling, general and administrative expenses is approximately $4.4 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)	2022	2021	2020
PK activator (PYRUKYND®)	$ 83,271	$ 73,999	$ 48,669
Novel PK activator (AG-946)	15,747	10,658	8,378
Other research and platform programs	26,837	22,959	13,790
Total direct research and development expenses	125,855	107,616	70,837
Compensation and related expenses	109,248	95,198	99,923
Facilities and IT related expenses & other	43,290	44,767	50,051
Other expenses - transition services	1,517	9,392	—
Total indirect research and development expenses	154,055	149,357	149,974
Total research and development expense	$ 279,910	$ 256,973	$ 220,811

Total Research and Development Expenses – 2022 vs. 2021 – The increase in research and development expenses of $22.9 million in 2022 compared to 2021 was due to a $18.2 million increase in our direct expenses and a $4.7 million increase in our indirect expenses. The increase in direct expenses was due to a $9.3 million increase in PYRUKYND® costs, a $5.1 million increase in AG-946 costs, and a $3.9 million increase in other research and platform programs. The increase in PYRUKYND® costs was primarily due to increased 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 AG-946 costs was primarily due to start-up costs for the phase 2 trial of AG-946 in patients with LR MDS and increased spend for the phase 1 trial of AG-946 in healthy volunteers and in patients with SCD. The increase in other research and platform programs was primarily driven by increased activity associated with our preclinical PAH program as well as increased activity on various other exploratory activities. The increase in indirect expenses was primarily due to a $14.1 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 $7.9 million of additional reimbursable transition related services we provided to Servier in 2021 compared to 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.

Total Research and Development Expenses – 2021 vs 2020 – The increase in research and development expenses of $36.2 million in 2021 compared to 2020 was primarily due to a $36.8 million increase in our direct expenses. The increase in direct expenses was primarily due to a $25.3 million increase in PYRUKYND® costs and a $9.2 million increase in other research and platform programs. The increase in PYRUKYND® costs was primarily due to startup costs for the initiated phase 3 trials of PYRUKYND®, ENERGIZE and ENERGIZE-T, and the phase 2/3 trial of PYRUKYND® in patients with SCD, RISE UP, offset by closeouts of ACTIVATE & ACTIVATE-T studies, and commercial launch preparation activities. The increase in other research and platform programs costs was primarily driven by planned increased activity on various exploratory activities. Included in total indirect research and development expenses was $9.4 million of reimbursable transition related services we provided to Servier related to the sale of the oncology business for discovery, clinical development, technical operations, and related activities which will continue for periods ranging from one month to approximately one year after March 31, 2021.

Other Income and Expense

(In thousands)	2022	2021	2020
Gain on sale of contingent payments	$ 127,853	$ —	$ —
Royalty income from gain on sale of oncology business	9,851	6,639	—
Interest income, net	12,793	836	6,611
Other income, net	6,749	14,433	—

Other Income and Expense – 2022 vs. 2021 – The $127.9 million gain on sale of contingent payments in 2022 was due to the October 27, 2022 sale of future contingent payments to entities affiliated with Sagard. The $12.0 million increase in interest income, net in 2022 compared to 2021 is primarily attributable to an increase in interest rates. The $3.2 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 2022 compared to 2021. The $7.7 million decrease in other income, net in 2022 compared to 2021 primarily related to approximately $13.8 million of reimbursable transition related services and fees for the sale of the oncology business

in 2021 compared to $2.6 million in 2022, partially offset by sublease income of $4.1 million in 2022 compared to $0.5 million in 2021.

Other Income and Expense – 2021 vs 2020 – The increase in other income, net in 2021 compared to 2020, primarily relates to approximately $13.8 million of reimbursable transition related services and fees for the sale of the oncology business for the year ended December 31, 2021. The increase in gain on sale of oncology business primarily relates to income from royalties on U.S. net sales of TIBSOVO® by Servier of approximately $6.6 million for the year ended December 31, 2021. The decrease in interest income, net is primarily attributable to a decrease in interest rates.

Loss from Operations and Net Income (Loss)

(In thousands)	2022	2021	2020
Net loss from continuing operations	$ (231,801)	$ (356,510)	$ (329,305)
Net income from discontinued operations, net of tax	—	1,961,225	1,935
Net (loss) income	(231,801)	1,604,715	(327,370)

Loss from Operations and Net (Loss) Income – 2022 vs 2021 – The $124.7 million decrease in net loss from continuing operations in 2022 compared to 2021 was primarily driven by the gain on sale of contingent payments in 2022 described above in Other Income and Expense, the increase in revenue in 2022 compared to 2021 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. These were partially offset by 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. The change in net income from discontinued operations and net (loss) income in 2022 compared to 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 income from discontinued operations.

Loss from Operations and Net Income (Loss) – 2021 vs 2020 – The increase in net loss from continuing operations in 2021 compared to 2020 was primarily driven by higher research and development expenses discussed above under Research and Development Expenses, partially offset by $13.9 million of reimbursable transition related services and fees related to the sale of the oncology business and a $6.6 million gain on sale of oncology business related to income from royalties on U.S. net sales of TIBSOVO® by Servier. The change in net income from discontinued operations and net income (loss) for the year ended December 31, 2021 compared to the year ended December 31, 2020 was primarily driven by the sale of our oncology business to Servier for approximately $1.8 billion in cash in the first quarter of 2021, which is included within net income from discontinued operations.

Liquidity and Capital Resources

Sources of liquidity

Since our inception, and through March 31, 2021, we 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 contingent payments to Sagard, proceeds from the sale of contingent payments 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. The milestone payment for approval of vorasidenib and royalty payments related to vorasidenib and TIBSOVO® represent contingent consideration. Servier also acquired our co-commercialization rights for BMS'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 below in Note 2, *Summary of Significant*

Accounting Policies, on October 27, 2022, we sold our rights to future contingent payments 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 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 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 December 31, 2022, we have not repurchased any shares under the Rule 10b-18 repurchase plan. In total, as of December 31, 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.

On April 30, 2020, we entered into an at-the-market sales agreement, or the 2020 sales agreement, with Cowen & Company LLC, or Cowen, pursuant to which we may offer and sell shares of our common stock having an aggregate offering price of up to $250.0 million through Cowen pursuant to a universal shelf registration statement on Form S-3 filed with the SEC on April 30, 2020. As of December 31, 2022, $250.0 million in common stock remained available for future issuance under the 2020 sales agreement. On February 15, 2023, we delivered written notice to Cowen that we were terminating the 2020 sales agreement, effective on February 22, 2023. As of the termination of the 2020 sales agreement, we had not sold any shares of our common stock under the 2020 sales agreement.

In addition to our cash, cash equivalents and marketable securities of $1.1 billion at December 31, 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, 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 prior to the loss of exclusivity of vorasidenib.

Cash flows

The following table provides information regarding our cash flows for the years ended December 31, 2022, 2021 and 2020:

(In thousands)	2022	2021	2020
Net cash used in operating activities	$ (309,478)	$ (407,320)	$ (290,759)
Net cash provided by investing activities	243,261	1,248,778	75,746
Net cash provided by (used in) financing activities	2,350	(765,768)	261,518
Net change in cash and cash equivalents	$ (63,867)	$ 75,690	$ 46,505

Net cash used in operating activities

Cash used in operating activities of $309.5 million during the year ended December 31, 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 $13.3 million, cash received related to interest income of $11.6 million and cash received from royalties on U.S. net sales of TIBSOVO® of $8.6 million.

Cash used in operating activities of $407.3 million during the year ended December 31, 2021, of which $314.1 million was used by continuing operations and $93.2 million was used by discontinued operations, was primarily due to operating expenses driven by research and development costs described above in Research and Development Expenses, offset by cash received of $39.5 million from sales of TIBSOVO®, and $1.2 million in cost reimbursements related to our collaboration agreements with Celgene.

Cash used in operating activities of $290.8 million during the year ended December 31, 2020, of which $243.9 million was used by continuing operations and $46.8 million was used by discontinued operations, was primarily due to operating expenses driven by research and development costs described above in Research and Development Expenses, offset by cash received of

$123.8 million from sales of TIBSOVO®, $7.9 million in royalty payments and $6.1 million in cost reimbursements related to our Collaboration Agreements with Celgene, $7.0 million in interest received, and $3.6 million in cost reimbursements related to our agreement with CStone Pharmaceuticals.

Net cash provided by investing activities

The cash provided by investing activities for the year ended December 31, 2022, of which all was provided by continuing operations, was primarily due to cash received of $131.8 million from the sale of future contingent payments described above in Other Income and Expense and higher proceeds from maturities and sales of marketable securities than purchases of marketable securities.

The cash provided by investing activities for the year ended December 31, 2021, of which $1,802.9 million was provided by discontinued operations and $554.2 million was used by continuing 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, and the result of higher purchases of marketable securities than proceeds from maturities and sales of marketable securities.

The cash provided by investing activities for the year ended December 31, 2020, of which $76.5 million was provided by continuing operations and $0.8 million was used by discontinued operations was primarily the result of lower purchases of marketable securities than proceeds from maturities and sales of marketable securities, offset by $14.9 million in purchases of property and equipment.

Net cash provided by (used in) financing activities

The cash provided by financing activities for the year ended December 31, 2022 was primarily due to $2.7 million of proceeds received from stock option exercises and purchases made pursuant to our employee stock purchase plan.

The cash used in financing activities for the year ended December 31, 2021 was primarily the due to the repurchase of common stock under our Repurchase Program of $802.5 million, partially offset by $37.3 million of proceeds received from stock option exercises and purchases made pursuant to our employee stock purchase plan.

The cash provided by financing activities for the year ended December 31, 2020 was primarily the result of net proceeds of $250.5 million from the sale of our tiered, sales-based royalty rights on worldwide net sales of IDHIFA® (enasidenib) and our ex-US regulatory milestones to Royalty Pharma in June 2020, and the $11.3 million of proceeds received from stock option exercises and purchases made pursuant to our employee stock purchase plan.

Funding requirements

We expect our expenses to increase as we continue the research, development and clinical trials of, seek marketing approvals for, and commercialize our product candidates in our rare disease portfolio, including as we continue to 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 December 31, 2022, together with anticipated product revenue and interest income will enable us to execute our operating plan, including funding our currently planned development programs for mitapivat, AG-946 and PAH, and commercializing mitapivat outside of the US through one or more partnerships, 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, the 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. 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.

Off-Balance Sheet Arrangements

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

Contractual Obligations

The following table summarizes our significant contractual obligations as of the payment due date by period at December 31, 2022:

	Payments due by period				
(In thousands)	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating lease obligations (1)	$ 99,203	$ 16,651	$ 38,167	$ 40,906	$ 3,479
Manufacturing arrangements (2)	904	301	603	—	—
Service arrangements (3)	9,300	1,860	3,720	3,720	—

(1) Relates to payment obligations under lease agreements covering approximately 146,000 square feet at 88 Sidney Street, 43,000 square feet at 64 Sidney Street, and 13,000 square feet at 38 Sidney Street, Cambridge, Massachusetts. All leases, as amended, expire on February 29, 2028. At the end of the initial lease period, we have the option to extend the leases at all facilities for two consecutive five year periods at the fair market rent at the time of the extension.

(2) Relates to payment obligations under a packaging and supply agreement for drug product.

(3) Relates to payment obligations under a development and manufacturing services agreement for drug product.

We enter into agreements in the normal course of business with CROs for clinical trials and contract manufacturing organizations, or CMOs, for supply manufacturing and with vendors for preclinical research studies and other services and products for operating purposes. These contractual obligations are cancelable at any time by us, generally upon prior written notice to the vendor, and are thus not included in the contractual obligations table. The service arrangement included in the table above is for a contractual term of five years, however, the total funds can be allocated in any manner to meet the agreement terms. Amounts included assume equal payments each year.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2022 and December 31, 2021, we had cash, cash equivalents and marketable securities of $1.1 billion and $1.3 billion, respectively, consisting 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 and CMOs that are located in Asia and Europe that are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these agreements. We do not currently hedge our foreign currency exchange rate risk. As of December 31, 2022 and December 31, 2021, we had minimal or no liabilities denominated in foreign currencies.

Item 8. Financial Statements and Supplementary Data

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. An index of those financial statements is found in Item 15, *Exhibits and Financial Statement Schedules*, of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and our principal financial officer, evaluated, as of the end of the period covered by this Annual Report on Form 10-K, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of December 31, 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 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 are 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 us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway

Commission (COSO) in its 2013 Internal Control – Integrated Framework. Based on our assessment, our management has concluded that, as of December 31, 2022, our internal control over financial reporting is effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2022, has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report, which is included herein.

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) during the fiscal quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item 10 will be included in our definitive proxy statement to be filed with the Securities and Exchange Commission, or SEC, with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 11. Executive Compensation

The information required by this Item 11 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and, other than the information required by Item 402(v) of Regulation S-K, is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item 12 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item 13 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services

The information required by this Item 14 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2023 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(1) Financial Statements

The following documents are included on pages F-1 through F-30 attached hereto and are filed as part of this Annual Report on Form 10-K.

(2) Financial Statement Schedules

Schedules have been omitted since they are either not required or not applicable or the information is otherwise included herein.

(3) Exhibits

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
2.1	Purchase and Sale Agreement, dated as of December 20, 2020, by and among the Registrant, Servier Pharmaceuticals, LLC, and, solely for purposes of guaranteeing certain obligations of the Purchaser, Servier S.A.S	8-K	001-36014	December 22, 2020	2.1	
2.2**	Purchase and Sale Agreement, dated October 27, 2022, by and among the Registrant, Sagard Healthcare Royalty Partners, LP and Sagard Healthcare Partners Co-Invest Designated Activity Company					X
3.1	Restated Certificate of Incorproation of the Registrant	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	
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1	333-189216	June 24, 2013	4.1	
4.2	Description of Securities Registered Under Section 12 of the Securities Exchange Act of 1934	10-K	001-36014	February 19, 2020	4.3	
10.1#	2007 Stock Incentive Plan	S-1	333-189216	June 10, 2013	10.1	
10.2#	Form of Incentive Stock Option Agreement under 2007 Stock Incentive Plan	S-1	333-189216	June 10, 2013	10.2	
10.3#	Form of Nonstatutory Stock Option Agreement under 2007 Stock Incentive Plan	S-1	333-189216	June 10, 2013	10.3	
10.4#	2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.4	
10.5#	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.5	

10.6#	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.6
10.7#	2013 Employee Stock Purchase Plan	S-1	333-189216	June 24, 2013	10.7
10.8	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-189216	July 11, 2013	10.12
10.9#	Letter Agreement, dated as of April 1, 2014, between the Registrant and Christopher Bowden, Ph.D.	10-K	001-36014	February 26, 2016	10.13
10.10	Lease, dated as of September 15, 2014, between the Registrant and Forest City 88 Sidney, LLC	8-K	001-36014	September 19, 2014	10.1
10.11	First Amendment to Lease for 88 Sidney Street, dated as of November 21, 2014, between the Registrant and Forest City 88 Sidney, LLC	8-K	001-36014	November 26, 2014	10.1
10.12#	Summary Description of Annual Cash Incentive Program	10-Q	001-36014	May 11, 2015	10.1
10.13	Second Amendment to Lease for 88 Sidney Street, dated July 20, 2015, by and between the Registrant and Forest City 88 Sidney Street, LLC	8-K	001-36014	July 23, 2015	10.1
10.14#	Form of Performance Share Unit Agreement under 2013 Stock Incentive Plan	10-K	001-36014	February 26, 2016	10.25
10.15	Lease, dated as of November 17, 2017, between the Registrant and UP 64 Sidney Street, LLC	8-K	001-36014	November 22, 2017	10.1
10.16	Third Amendment to Lease for 88 Sidney Street, dated November 17, 2017, by and between the Registrant and Forest City 88 Sidney Street, LLC	8-K	001-36014	November 22, 2017	10.2
10.17	First Amendment of Lease, dated April 11, 2018, by and between UP 64 Sidney Street, LLC and Agios Pharmaceuticals. Inc.	8-K	001-36014	April 13, 2018	10.1
10.18#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for employees)	10-Q	001-36014	May 4, 2018	10.1
10.19#	Letter Agreement, dated as of August 30, 2018, between the Registrant and Jacqualyn A. Fouse, Ph.D.	10-Q	001-36014	November 1, 2018	10.2
10.20#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for directors)	10-K	001-36014	February 14, 2019	10.32
10.21	Lease, dated as of April 11, 2019, by and between the Registrant and Thirty-Eight Sidney Street Limited LLC	10-Q	001-36014	August 1, 2019	10.1
10.22	Fourth Amendment to Lease, dated as of April 11, 2019, by and between the Registrant and Forest City 88 Sidney Street, LLC	10-Q	001-36014	August 1, 2019	10.2
10.23	Third Amendment of Lease, dated as of April 11, 2019, by and between the Registrant and UP 64 Sidney Street, LLC	10-Q	001-36014	August 1, 2019	10.3
10.24#	Letter Agreement, dated as of September 17, 2019, between the Registrant and Jonathan Biller	10-K	001-36014	February 19, 2020	10.35

10.25#	Letter Agreement, dated as of October 7, between the Registrant and Bruce Car	10-Q	001-36014	April 30, 2020	10.1	
10.26	Sales Agreement, dated April 30, 2020, by and between the Registrant and Cowen and Company, LLC	S-3ASR	333-237930	April 30, 2020	1.2	
10.27	Sublease Agreement, dated July 27, 2021, between the Registrant and Prime Medicine, Inc. (38 Sidney Street)	10-Q	001-36014	November 3, 2021	10.2	
10.28	Sublease Agreement, dated July 27, 2021, between the Registrant and Prime Medicine, Inc. (64 Sidney Street)	10-K	001-36014	February 24, 2022	10.44	
10.29#	Letter Agreement, dated July 8, 2022, between the Registrant and Brian Goff	10-Q	001-36014	August 4, 2022	10.2	
10.30#	Form of Inducement Stock Option Agreement for Brian Goff	10-Q	001-36014	August 4, 2022	10.3	
10.31#	Form of Inducement Restricted Stock Unit Agreement for Brian Goff	10-Q	001-36014	August 4, 2022	10.4	
10.32#**	Form of Inducement Performance Stock Unit Agreement for Brian Goff	10-Q	001-36014	August 4, 2022	10.5	
10.33#	Letter Agreement, dated as of September 16, 2022, between the Registrant and Cecilia Jones	10-Q	001-36014	November 3, 2022	10.5	
10.34#	Form of Inducement Stock Option Agreement for Cecilia Jones	S-8	333- 267624	September 26, 2022	99.1	
10.35#	Form of Inducement Restricted Stock Unit Agreement for Cecilia Jones	S-8	333- 267624	September 26, 2022	99.2	
10.36#**	Form of Inducement Performance Stock Unit Agreement for Cecilia Jones	S-8	333- 267624	September 26, 2022	99.3	
10.37#	Amended and Restated Severance Benefits Plan	8-K	001-36014	October 7, 2022	10.1	
10.38#	Letter Agreement, dated as of December 5, 2022, between the Registrant and Tsveta Milanova					X
10.39#	Form of Inducement Stock Option Agreement for Tsveta Milanova	S-8	333- 269018	January 3, 2023	99.1	
10.40#	Form of Inducement Restricted Stock Unit Agreement for Tsveta Milanova	S-8	333- 269108	January 3, 2023	99.2	
10.41#**	Form of Inducement Performance Stock Unit Agreement for Tsveta Milanova	S-8	333- 269108	January 3, 2023	99.3	
10.42#	Consulting Agreement, dated May 23, 2022, by and between the Registrant and Bruce Car	10-Q	001-36014	August 4, 2022	10.1	
10.43#	Consulting Agreement, dated January 1, 2023, by and between the Registrant and Richa Poddar					X
21.1	Subsidiaries of the Registrant					X
23.1	Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm					X
31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended					X

31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.	X
32.1*	Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	X
32.2*	Certification of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	X
101.INS	XBRL Instance Document	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)	X

#	Indicates management contract or compensatory plan or arrangement.
*	This certification will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.
**	Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) 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.

February 23, 2023

By: /s/ Brian Goff
Brian Goff
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Brian Goff Brian Goff	Chief Executive Officer (Principal executive officer)	February 23, 2023
/s/ Cecilia Jones Cecilia Jones	Chief Financial Officer (Principal financial officer)	February 23, 2023
/s/ T.J. Washburn T.J. Washburn	Vice President, Controller (Principal accounting officer)	February 23, 2023
/s/ Jacqualyn A. Fouse Jacqualyn A. Fouse, Ph.D.	Chair of the Board of Directors	February 23, 2023
/s/ Rahul Ballal Rahul Ballal, Ph.D.	Director	February 23, 2023
/s/ Paul J. Clancy Paul J. Clancy	Director	February 23, 2023
/s/ Kaye Foster Kaye Foster	Director	February 23, 2023
/s/ Maykin Ho Maykin Ho, Ph.D.	Director	February 23, 2023
/s/ John M. Maraganore John M. Maraganore, Ph.D.	Director	February 23, 2023
/s/ David Scadden David Scadden, M.D.	Director	February 23, 2023
/s/ David P. Schenkein David P. Schenkein, M.D.	Director	February 23, 2023
/s/ Cynthia Smith Cynthia Smith	Director	February 23, 2023

Agios Pharmaceuticals, Inc.

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of Agios Pharmaceuticals, Inc.

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Agios Pharmaceuticals, Inc. and its subsidiaries (the "Company") as of December 31, 2022 and 2021, and the related consolidated statements of operations, of comprehensive income (loss), of stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2022, including the related notes (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2022, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021**,** and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2022, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Annual Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed 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. A company's internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (ii) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (iii) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or

disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accounting for the Sagard agreement

As described in Note 1 to the consolidated financial statements, the consideration for the sale of the Company's oncology business to Servier includes a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity, referred to as contingent payments. The Company recognizes the contingent payments in the royalty income from gain on sale of oncology business line item in the consolidated statement of operations in the period when realizable. On October 27, 2022, the Company sold their rights to future contingent payments, to entities affiliated with Sagard Healthcare Partners, or Sagard, and recognized income of $127.9 million within the gain on sale of contingent payments line item in the consolidated statement of operations for the year ended December 31, 2022.

The principal considerations for our determination that performing procedures relating to accounting for the Sagard agreement is a critical audit matter are (i) the significant judgment by management when determining the appropriate accounting for the sale of the rights to future contingent payments, and (ii) a high degree of auditor judgment and effort in performing procedures and evaluating audit evidence related to management's assessment of the accounting analysis and conclusions for the Sagard agreement.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls related to management's accounting analysis and conclusions, including controls over management's assessment of the terms and conditions of the Sagard agreement. These procedures also included, among others, (i) reviewing the terms and conditions in the Sagard agreement, and (ii) evaluating management's assessment of the accounting analysis and conclusions, including evaluating the impact of legal considerations.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
February 23, 2023

We have served as the Company's auditor since 2017.

Agios Pharmaceuticals, Inc.

Consolidated Balance Sheets

(In thousands, except share and per share data) December 31:	2022	2021
Assets		
Current assets:		
Cash and cash equivalents	$ 139,259	$ 203,126
Marketable securities	643,860	816,892
Accounts receivable, net	2,206	—
Other receivable	—	4,378
Inventory	8,492	—
Prepaid expenses and other current assets	38,955	39,835
Total current assets	832,772	1,064,231
Marketable securities	313,874	266,375
Operating lease assets	65,129	75,124
Property and equipment, net	22,987	28,923
Financing lease assets	—	183
Other non-current assets	3,956	2,900
Total assets	$ 1,238,718	$ 1,437,736
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 18,616	$ 16,700
Accrued expenses	30,350	31,967
Operating lease liabilities	13,663	10,828
Financing lease liabilities	—	331
Total current liabilities	62,629	59,826
Operating lease liabilities, net of current portion	71,996	85,659
Financing lease liabilities, net of current portion	—	276
Other non-current liabilities	3,279	—
Total liabilities	137,904	145,761
Commitments and contingent liabilities (Note 16)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 25,000,000 shares authorized, no shares issued and outstanding at December 31, 2022 and 2021	—	—
Common stock, $0.001 par value; 125,000,000 shares authorized; 71,256,118 shares issued and 55,039,707 outstanding at December 31, 2022 and 70,550,631 shares issued and 54,334,220 outstanding at December 31, 2021	71	71
Additional paid-in capital	2,386,325	2,334,348
Accumulated other comprehensive loss	(12,535)	(1,198)
Accumulated deficit	(470,561)	(238,760)
Treasury stock, at cost (16,216,411 shares at December 31, 2022 and December 31, 2021)	(802,486)	(802,486)
Total stockholders' equity	1,100,814	1,291,975
Total liabilities and stockholders' equity	$ 1,238,718	$ 1,437,736

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Operations

(In thousands, except share and per share data) Years Ended December 31:	2022	2021	2020
Revenues:			
Product revenue, net	$ 11,740	$ —	$ —
Milestone revenue	2,500	—	—
Total revenue	14,240	—	—
Operating expenses			
Cost of sales	$ 1,704	$ —	$ —
Research and development	279,910	256,973	220,811
Selling, general and administrative	121,673	121,445	115,105
Total operating expenses	403,287	378,418	335,916
Loss from operations	(389,047)	(378,418)	(335,916)
Gain on sale of contingent payments	127,853	—	—
Royalty income from gain on sale of oncology business	9,851	6,639	—
Interest income, net	12,793	836	6,611
Other income, net	6,749	14,433	—
Net loss from continuing operations	(231,801)	(356,510)	(329,305)
Net income from discontinued operations, net of tax	—	1,961,225	1,935
Net (loss) income	$ (231,801)	$ 1,604,715	$ (327,370)
Net loss from continuing operations per share - basic and diluted	$ (4.23)	$ (5.90)	$ (4.77)
Net income from discontinued operations per share - basic and diluted	$ —	$ 32.45	$ 0.03
Net (loss) income per share - basic and diluted	$ (4.23)	$ 26.55	$ (4.74)
Weighted-average number of common shares used in computing net loss per share from continuing operations, net income per share from discontinued operations and net (loss) income per share – basic and diluted	54,789,435	60,447,346	68,997,879

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Comprehensive (Loss) Income

(In thousands) Years Ended December 31:	2022	2021	2020
Net (loss) income	$ (231,801)	$ 1,604,715	$ (327,370)
Other comprehensive (loss) income			
Unrealized loss on available-for-sale securities	(11,337)	(1,303)	(97)
Comprehensive (loss) income	$ (243,138)	$ 1,603,412	$ (327,467)

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Stockholders' Equity

(In thousands, except share amounts)	Common Stock Shares	Common Stock Amount	Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Treasury Shares	Treasury Amount	Total Stockholders' Equity
Balance at December 31, 2019	68,401,105	$ 68	$ 2,156,363	$ 202	$ (1,516,105)	—	$ —	$ 640,528
Unrealized loss on available-for-sale securities	—	—	—	(97)	—	—	—	(97)
Net loss	—	—	—	—	(327,370)	—	—	(327,370)
Stock-based compensation expense	—	—	61,602	—	—	—	—	61,602
Issuance of common stock under stock incentive and employee stock purchase plans	892,815	1	11,316	—	—	—	—	11,317
Disposition of oncology business	—	—	13,520	—	—	—	—	13,520
Balance at December 31, 2020	69,293,920	$ 69	$ 2,242,801	$ 105	$ (1,843,475)	—	$ —	$ 399,500
Unrealized loss on available-for-sale securities	—	—	—	(1,303)	—	—	—	(1,303)
Net income	—	—	—	—	1,604,715	—	—	1,604,715
Stock-based compensation expense	—	—	53,508	—	—	—	—	53,508
Issuance of common stock under stock incentive and employee stock purchase plans	1,256,711	2	37,294	—	—	—	—	37,296
Repurchase of common stock	—	—	—	—	—	(16,216,411)	(802,486)	(802,486)
Disposition of oncology business	—	—	745	—	—	—	—	745
Balance at December 31, 2021	70,550,631	$ 71	$ 2,334,348	$ (1,198)	$ (238,760)	(16,216,411)	$ (802,486)	$ 1,291,975
Unrealized loss on available-for-sale securities	—	—	—	(11,337)	—	—	—	(11,337)
Net loss	—	—	—	—	(231,801)	—	—	(231,801)
Stock-based compensation expense	—	—	49,296	—	—	—	—	49,296
Issuance of common stock under stock incentive and employee stock purchase plans	705,487	—	2,681	—	—	—	—	2,681
Balance at December 31, 2022	71,256,118	$ 71	$ 2,386,325	$ (12,535)	$ (470,561)	(16,216,411)	$ (802,486)	$ 1,100,814

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows

(In thousands) Years Ended December 31:	2022	2021	2020
Operating activities			
Net (loss) income	$ (231,801)	$ 1,604,715	$ (327,370)
Less: Net income from discontinued operations	—	1,961,225	1,935
Net loss from continuing operations	(231,801)	(356,510)	(329,305)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	8,564	9,240	9,790
Stock-based compensation expense	49,296	53,508	61,602
Net (accretion of discount) amortization of premium on marketable securities	(1,198)	6,949	3,022
Gain on sale of contingent payments	(127,853)	—	—
(Gain) loss on disposal of property and equipment	(48)	12	—
Non-cash operating lease expense	9,995	9,537	8,982
Changes in operating assets and liabilities:			
Accounts receivable, net	(2,206)	—	—
Inventory	(8,492)	—	—
Other receivables	447	(4,378)	—
Prepaid expenses and other current and non-current assets	(176)	(26,846)	(3)
Accounts payable	3,436	1,863	3,330
Accrued expenses	(1,617)	66	6,765
Operating lease liabilities	(10,828)	(7,527)	(8,127)
Other liabilities	3,003	—	—
Net cash used in operating activities	(309,478)	(314,086)	(243,944)
Net cash used in operating activities - discontinued operations	—	(93,234)	(46,815)
Net cash used in operating activities	(309,478)	(407,320)	(290,759)
Investing activities			
Purchases of marketable securities	(1,030,781)	(1,378,221)	(557,030)
Proceeds from maturities and sales of marketable securities	1,146,175	829,804	647,685
Proceeds from sale of contingent payments	131,784	—	—
Purchases of property and equipment	(4,881)	(5,741)	(14,106)
Proceeds from sale of equipment	964	—	—
Net cash provided by (used in) investing activities	243,261	(554,158)	76,549
Net cash provided by (used in) investing activities - discontinued operations	—	1,802,936	(803)
Net cash provided by investing activities	243,261	1,248,778	75,746
Financing activities			
Payments on financing lease obligations	(331)	(578)	(336)
Purchase of treasury stock	—	(802,486)	—
Net proceeds from stock option exercises and employee stock purchase plan	2,681	37,296	11,317
Net cash provided by (used in) financing activities	2,350	(765,768)	10,981
Net cash provided by financing activities - discontinued operations	—	—	250,537
Net cash provided by (used in) financing activities	2,350	(765,768)	261,518
Net change in cash and cash equivalents	(63,867)	75,690	46,505
Cash and cash equivalents at beginning of the period	203,126	127,436	80,931
Cash and cash equivalents at end of the period	$ 139,259	$ 203,126	$ 127,436
Supplemental disclosure of non-cash investing and financing transactions:			
Additions to property and equipment in accounts payable and accrued expenses	$ 158	$ 1,678	$ 465
Cash taxes paid	$ —	$ 16,078	$ —
Financing lease liabilities arising from obtaining financing lease assets	$ —	$ 511	$ —

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

Note 1. Nature of Business

References to Agios

Throughout this Annual Report on Form 10-K, "the Company," "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 diseases. 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 rare diseases. We are located in Cambridge, Massachusetts.

The lead product candidate in our portfolio, PYRUKYND® (mitapivat), is an activator of both wild-type and mutant pyruvate kinase, or PK, enzymes for the potential treatment of hemolytic anemias. In February 2022, the Food and Drug Administration, or FDA, approved PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. In November 2022, we received marketing authorization from the European Commission for PYRUKYND® for the treatment of PK deficiency in adult patients in the European Union, or EU. In December 2022, we received marketing authorization in Great Britain for PYRUKYND® for the treatment of PK deficiency in adult patients under the European Commission Decision Reliance Procedure. 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, or LR MDS, and hemolytic anemias.

In addition to the aforementioned clinical development programs, we continue to invest in our late-stage research program focused on advancing a phenylalanine hydroxylase, or PAH, stabilizer for the treatment of phenylketonuria, or PKU.

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, or Celgene, and following the sale Servier will conduct certain clinical development activities within the IDHIFA® development program.

We recorded income from royalties of approximately $9.9 million and $6.6 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 consolidated statements of operations, for the years ended December 31, 2022 and December 31, 2021, respectively.

Sale of Contingent Payments

The consideration for the sale of our oncology business to Servier includes a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity, referred to as contingent payments. We recognize the contingent payments in the royalty income from gain on sale of oncology business line item in our consolidated statement of operations in the period when realizable. On October 27, 2022, we sold our rights to future contingent payments to entities affiliated with Sagard Healthcare Partners, or Sagard, and recognized income of $127.9 million within the gain on sale of contingent payments line item in our consolidated statements of operations for the year ended December 31, 2022. We retained our rights to the potential milestone payment and royalties from Servier if vorasidenib is approved by the FDA.

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.

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 under the Repurchase Program. We have not repurchased any shares of common stock in fiscal year 2022 and as of December 31, 2022 we have 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 December 31, 2022, we have not repurchased any shares under the Rule 10b-18 repurchase plan. In total, as of December 31, 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.

On April 30, 2020, we entered into an at-the-market sales agreement, or the 2020 sales agreement, with Cowen & Company LLC, or Cowen, pursuant to which we may offer and sell shares of our common stock having an aggregate offering price of up to $250.0 million through Cowen pursuant to a universal shelf registration statement on Form S-3 filed with the SEC on April 30, 2020. As of December 31, 2022, $250.0 million in common stock remained available for future issuance under the 2020 sales agreement. On February 15, 2023, we delivered written notice to Cowen that we were terminating the 2020 sales agreement, effective on February 22, 2023. As of the termination of the 2020 sales agreement, we had not sold any shares of our common stock under the 2020 sales agreement.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of $1.1 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 to be sufficient to fund current operations for at least the next twelve months from the issuance of the financial statements. If we are unable to raise additional funds through equity or debt financings, we may be required to delay, limit, reduce or terminate product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Note 2. Summary of Significant Accounting Policies

Principles of consolidation

The consolidated financial statements include our accounts and the accounts of our wholly owned subsidiaries, Agios Securities Corporation, Agios International Sarl (GmbH), Agios Germany GmbH, Agios Netherlands B.V., Agios Italy S.R.L., Agios France SARL, and Agios Limited. All intercompany transactions have been eliminated in consolidation. The consolidated financial statements have been prepared in conformity with U.S. generally accepted accounting principles, or U.S. GAAP.

Use of estimates

The preparation of our 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.

Cash and cash equivalents

We consider highly liquid investments with a maturity of three months or less when purchased to be cash equivalents. Cash equivalents are stated at fair value.

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 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 twelve months ended December 31, 2022 were expensed prior to February 17, 2022 and, therefore, are not included in costs of sales during the twelve months ended December 31, 2022.

Marketable securities

Marketable securities at December 31, 2022 and 2021 consisted of investments in U.S. Treasuries, government securities and corporate debt securities. We determine the appropriate classification of the securities at the time they are acquired and evaluate the appropriateness of such classifications at each balance sheet date. We classify our marketable securities as available-for-sale pursuant to ASC 320, *Investments – Debt and Equity Securities*. Marketable securities are recorded at fair value. Unrealized gains and losses are included as a component of accumulated other comprehensive (loss) income in the consolidated balance sheets and statements of stockholders' equity and a component of total comprehensive (loss) income in the consolidated statements of comprehensive (loss) income, until realized. Realized gains and losses are included in investment income on a specific-identification basis.

At December 31, 2022 and 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 one to two years, and (ii) we do not intend to liquidate within the next twelve months, although these funds are available for use and therefore classified as available-for-sale.

We review marketable securities for impairment whenever the fair value of a marketable security is less than the amortized cost and evidence indicates that a marketable security's carrying amount is not recoverable. Unrealized losses are evaluated for impairment under ASC 326, *Financial Instruments - Credit Losses*, to determine if the impairment is credit-related or noncredit-related. Credit-related impairment is recognized as an allowance on the balance sheet with a corresponding adjustment to earnings, and noncredit-related impairment is recognized in other comprehensive (loss) income, net of taxes. Evidence considered in this assessment includes reasons for the impairment, compliance with our investment policy, the severity of the impairment, collectability of the security, and any adverse conditions specifically related to the security, an industry, or geographic area.

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, either 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.

Our financial assets, which include cash equivalents and marketable securities, have been initially valued at the transaction price, and subsequently revalued at the end of each reporting period, 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 December 31, 2022 or 2021. Fair value information for these assets, including their classification in the fair value hierarchy is included in Note 3, *Fair Value Measurements***.**

There have been no changes to the valuation methods during the years ended December 31, 2022 and 2021. We evaluate transfers between levels at the end of each reporting period.

The carrying amounts of other receivables, prepaid expenses and other current assets, accounts payable, and accrued expenses approximate their fair values due to their short-term maturities.

Concentrations of credit risk

Financial instruments which potentially subject us to credit risk consist primarily of cash, cash equivalents, and marketable securities. We hold these investments in highly rated financial institutions, and, by policy, limit the amounts of credit exposure to any one financial institution. These amounts at times may exceed federally insured limits. We have not experienced any credit losses in such accounts and do not believe we are exposed to any significant credit risk on these funds. We have no off-balance sheet concentrations of credit risk, such as foreign currency exchange contracts, option contracts, or other hedging arrangements.

Property and equipment

Property and equipment consist of laboratory equipment, computer equipment and software, leasehold improvements, furniture and fixtures, and office equipment. Costs of major additions and betterment are capitalized; maintenance and repairs, which do not improve or extend the life of the respective assets, are charged to expense as incurred. Upon retirement or sale, the cost of the disposed asset and the related accumulated depreciation are removed from the accounts and the resulting gain or loss is recognized.

Property and equipment is stated at cost, and depreciated using the straight-line method over the estimated useful lives of the respective assets:

	Years
Laboratory equipment	5
Computer equipment and software	3
Furniture and fixtures	5
Office equipment	5

Leasehold improvements are amortized over the lesser of the remaining lease term or the estimated useful life of the improvement.

Impairment of long-lived assets

We periodically evaluate our long-lived assets for potential impairment in accordance with ASC 360, *Property, Plant and Equipment*. Potential impairment is assessed when there is evidence that events or changes in circumstances indicate that the carrying amount of an asset may not be recovered. Recoverability of these assets is assessed based on the undiscounted expected future cash flows from the assets, considering a number of factors, including past operating results, budgets and

economic projections, market trends and product development cycles. If impairments are identified, assets are written down to their estimated fair value. We did not recognize any impairment charges through December 31, 2022.

Leases

We determine if an arrangement is a lease at inception. An arrangement is determined to contain a lease if the contract conveys the right to control the use of an identified property or equipment for a period of time in exchange for consideration. If we can benefit from the various underlying assets of a lease on their own or together with other resources that are readily available, or if the various underlying assets are neither highly dependent on nor highly interrelated with other underlying assets in the arrangement, they are considered to be a separate lease component. In the event multiple underlying assets are identified, the lease consideration is allocated to the various components based on each of the component's relative fair value.

Operating lease assets represent our right to use an underlying asset for the lease term and operating lease liabilities represent our obligation to make lease payments arising from the leasing arrangement. Operating lease assets and operating lease liabilities are recognized at commencement date based on the present value of lease payments over the lease term. As most of our leases do not provide an implicit rate, in determining the operating lease liabilities we use an estimate of our incremental borrowing rate. The incremental borrowing rate is determined using two alternative credit scoring models to estimate our credit rating, adjusted for collateralization. The calculation of the operating lease assets includes any lease payments made and excludes any lease incentives. Our lease terms may include options to extend or terminate the lease when it is reasonably certain that we will exercise that option.

For operating leases, we record operating lease assets and lease liabilities in our consolidated balance sheets. Lease expense for lease payments is recognized on a straight-line basis over the lease term. Short-term leases, or leases that have a lease term of 12 months or less at commencement date, are excluded from this treatment and are recognized on a straight-line basis over the term of the lease.

We have not entered into any material short-term leases or financing leases as of December 31, 2022.

Research and development costs

Research and development costs, including those accrued as of each balance sheet date, are expensed as incurred. These costs include salaries and personnel-related costs, consulting fees, fees paid for contract research services, fees paid to contract research organizations, or CROs, and other third parties in connection with clinical trials and preclinical development activities, fees paid to investigative sites in connection with clinical studies, the costs associated with the product manufacturing, development, and distribution of clinical supplies, the costs of laboratory equipment and facilities, and other external costs.

Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. Additionally, there may be instances in which payments made to our vendors will exceed the level of services provided, and result in a prepayment of the research and development expense. The capitalized amounts are expensed as the related goods are delivered or the services are performed. We estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly.

Stock-based compensation

We account for stock-based compensation awards in accordance with ASC 718, *Compensation –Stock Compensation*, or ASC 718. For stock-based awards granted to employees, non-employees and members of the board of directors for their services and for participation in our employee stock purchase plan, we estimate the grant date fair value of each option award using the Black-Scholes option-pricing model. The use of the Black-Scholes option-pricing model requires us to make assumptions with respect to the expected term of the option, the expected volatility of the common stock consistent with the expected life of the option, risk-free interest rates and expected dividend yields of the common stock. For awards subject to service-based vesting conditions, we recognize stock-based compensation expense equal to the grant date fair value of stock options on a straight-line basis over the requisite service period. For awards subject to both performance and service-based vesting conditions, we recognize stock-based compensation expense over the remaining service period if the performance condition is considered probable of achievement using management's best estimates.

Income taxes

Income taxes are recorded in accordance with ASC 740, *Accounting for Income Taxes*, or ASC 740, which provides for deferred taxes using an asset and liability approach. We recognize deferred tax assets and liabilities for the expected future tax consequences of events that have been included in our financial statements or tax returns. We determine our deferred tax assets and liabilities based on differences between the financial reporting and tax bases of assets and liabilities, which are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are

provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

We also account for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, we recognize the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances.

Comprehensive income (loss)

Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions, and other events and circumstances, and currently consists of net loss and unrealized gains and losses on available-for-sale securities. Accumulated other comprehensive (loss) income consists entirely of unrealized gains and losses from available-for-sale securities as of December 31, 2022 and 2021.

Net income (loss) per share

Basic net income (loss) per share is calculated by dividing net income (loss) by the weighted-average shares outstanding during the period, without consideration for common stock equivalents. Diluted net income (loss) per share is calculated by adjusting 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 income (loss) per share calculation, stock options, restricted stock units, or RSUs, performance-based stock units, or PSUs, and market-based stock units, or MSUs, for which the performance and market vesting conditions, respectively, have been deemed probable, and employee stock purchase plan shares are considered to be common stock equivalents but are excluded from the calculation of diluted net income (loss) per share as their effect would be anti-dilutive.

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

Segment and geographic information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker or decision-making group in making decisions on how to allocate resources and assess performance. Our chief operating decision maker is the chief executive officer. Our chief operating decision maker and we view our operations and manage our business as one operating segment.

Discontinued operations

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

Due to the sale of the oncology business during the first quarter of 2021, in accordance with ASC 205, we have classified the results of the oncology business as discontinued operations in our consolidated statements of operations and cash flows for all periods presented, and refer to Note 15, *Discontinued Operations*. All assets and liabilities associated with our oncology business were therefore classified as assets and liabilities of discontinued operations in our consolidated balance sheets for the periods presented. All amounts included in the notes to the consolidated financial statements relate to continuing operations unless otherwise noted.

Treasury stock

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

Recent accounting pronouncements

In June 2016, the Financial Accounting Standards Board, or FASB, issued ASU 2016-13, *Financial Instruments - Credit Losses (Topic 326)*, which introduces new guidance for the accounting for credit losses on instruments within its scope. The new guidance introduces an approach based on expected losses to estimate credit losses on certain types of financial instruments. Credit losses relating to available-for-sale debt securities will also be recorded through an allowance for credit losses rather than as a reduction in the amortized cost basis of the securities. The guidance is effective for fiscal years beginning after December 31, 2019, including interim periods within those years. The Company adopted this amendment as of January 1, 2020, which eliminated the concept of other-than-temporary impairments and required credit losses on debt securities to be recorded through an allowance for credit losses instead of as a reduction in the amortized cost basis of the securities. Application of the amendments is through a cumulative-effect adjustment to retained earnings as of the effective date. There was no material impact to the Company's consolidated financial position, results of operation, or cash flows.

Other accounting standards that have been issued by the FASB 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.

Subsequent events

We considered events or transactions occurring after the balance sheet date, but prior to the issuance of the consolidated financial statements, for potential recognition or disclosure in our consolidated financial statements. All significant subsequent events have been properly disclosed in the consolidated financial statements.

Note 3. Fair Value Measurements

The following table summarizes our cash equivalents and marketable securities measured at fair value and by level (as described in Note 2. *Summary of Significant Accounting Policies*) on a recurring basis as of December 31, 2022:

(In thousands)	Level 1	Level 2	Level 3	Total
Cash equivalents	$ 37,093	$ 50,909	$ —	$ 88,002
Total cash equivalents	37,093	50,909	—	88,002
Marketable securities:				
U.S. Treasuries	—	84,596	—	84,596
Government securities	—	331,443	—	331,443
Corporate debt securities	—	541,695	—	541,695
Total marketable securities	—	957,734	—	957,734
Total cash equivalents and marketable securities	$ 37,093	$ 1,008,643	$ —	$ 1,045,736

There were no transfers between Level 1 and Level 2 and we had no financial assets or liabilities that were classified as Level 3 at any point during the year ended December 31, 2022.

Note 4. Marketable Securities

Marketable securities at December 31, 2022 consisted of the following:

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
U.S. Treasuries	$ 68,175	$ 3	$ (811)	$ 67,367
Government securities	220,901	8	(5,289)	215,620
Corporate debt securities	363,263	1	(2,391)	360,873
Total Current	652,339	12	(8,491)	643,860
Non-current:				
U.S. Treasuries	17,418	4	(193)	17,229
Government securities	117,475	7	(1,659)	115,823
Corporate debt securities	183,037	76	(2,291)	180,822
Total Non-current	317,930	87	(4,143)	313,874
Total marketable securities	$ 970,269	$ 99	$ (12,634)	$ 957,734

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

There were no material realized gains or losses on marketable securities for the years ended December 31, 2022 and 2021.

At December 31, 2022 and 2021, we held 259 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 December 31, 2022 and December 31, 2021 related to these securities. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2022 and 2021 was $868.2 million and $950.5 million, respectively. There were no individual securities that were in a significant unrealized loss position as of December 31, 2022 and 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 December 31, 2022 and 2021.

Note 5. Inventory

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

(In thousands)	December 31, 2022	December 31, 2021
Raw materials	$ —	$ —
Work-in-process	7,550	—
Finished goods	942	—
Total inventory	$ 8,492	$ —

Note 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 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.

On April 11, 2019, we entered into an agreement to lease approximately 13,000 square feet of office space located at 38 Sidney Street, Cambridge, Massachusetts, or the 38 Sidney Lease, with Thirty-Eight Sidney Street, LLC. The initial term of the 38 Sidney Lease commenced on May 1, 2019 and expires on February 29, 2028. At the end of the lease term, we have the option to extend the 38 Sidney Lease for two consecutive terms of five years at fair market rent at the time of the extension. The 38 Sidney Lease provides us with the right to lease additional space within the 38 Sidney Street building and also includes rent escalation clauses and a tenant improvement allowance of $1.0 million.

In connection with the 38 Sidney Lease, we also amended our existing building leases at 88 Sidney Street, Cambridge, Massachusetts and at 64 Sidney Street, Cambridge, Massachusetts to extend the initial terms of those leases by approximately three years through February 29, 2028. The amendments also provide us with the right to lease additional space at the 64 Sidney Street building. Our existing extension options for the 88 Sidney Street building and 64 Sidney Street building continue as set forth in the existing leases for those buildings.

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

(In millions)	2022	2021	2020
Operating lease costs	$ 15,227	$ 15,229	$ 15,241
Cash paid for amounts included in the measurement of operating lease liabilities	17,035	14,411	14,424

We have not entered into any material short-term leases or financing leases as of December 31, 2022.

In arriving at the operating lease liabilities as of December 31, 2022, we applied the weighted-average incremental borrowing rate of 5.7% from inception over a weighted-average remaining lease term of 5.2 years. In arriving at the operating lease liabilities as of December 31, 2021, we applied the weighted-average incremental borrowing rate of 5.7% over a weighted-average remaining lease term of 6.2 years.

As of December 31, 2022, undiscounted minimum rental commitments under non-cancelable leases, for each of the next five years and total thereafter, were as follows:

(In thousands)		
2023	$	16,651
2024		18,660
2025		19,507
2026		20,151
2027		20,755
Thereafter		3,479
Undiscounted minimum rental commitments		99,203
Interest		(13,544)
Total operating lease liabilities	$	85,659

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 $4.1 million and $0.5 million for the years ended December 31, 2022 and December 31, 2021, respectively, in other income, net in the 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 consolidated balance sheet.

As of December 31, 2022, the future minimum lease payments to be received under the long-term sublease agreements were as follows:

(In thousands)		
2023		4,329
2024		4,459
2025		1,101
Total	$	9,889

Note 7. Accrued Expenses

Accrued expenses consisted of the following at December 31:

(In thousands)	2022	2021
Accrued compensation	$ 18,105	$ 19,818
Accrued research and development costs	8,425	5,980
Accrued professional fees	2,435	2,335
Accrued other	1,385	3,834
Total accrued expenses	$ 30,350	$ 31,967

Note 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, was as follows for the years ended December 31:

(In thousands)	2022	2021	2020
Product revenue, net	$ 11,740	$ —	$ —

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.

The following table summarizes balances and activity in each of the product revenue allowance and reserve categories for the year ended December 31, 2022:

(In thousands)	Contractual Adjustments	Government Rebates	Returns	Total
Balance at December 31, 2021	$ —	$ —	$ —	$ —
Current provisions relating to sales in the current year	497	912	133	1,542
Adjustments relating to prior years	—	—	—	—
Payments/returns relating to sales in the current year	(432)	(339)		(771)
Payments/returns relating to sales in the prior years	—	—	—	—
Balance at December 31, 2022	$ 65	$ 573	$ 133	$ 771

There were no balances or activity related to product revenue allowance and reserve categories for the year ended December 31, 2021.

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

(In thousands)	December 31, 2022	December 31, 2021
Reduction of accounts receivable	$ 60	$ —
Component of accrued expenses	711	—
Total revenue-related reserves	$ 771	$ —

The following table presents changes in our contract assets during the year ended December 31, 2022:

(In thousands)	December 31, 2021	Additions	Deductions	December 31, 2022
Contract assets[1]				
Accounts receivable, net	$ —	$ 13,283	$ (11,077)	$ 2,206

(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.

There were no balances or activity related to contract assets for the year ended December 31, 2021.

Note 9. Share-Based Payments

Stock incentive plans

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, RSUs, 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 December 31, 2022, the total number of shares reserved under the 2007 Plan and the 2013 Plan was 12,821,789, and we had 5,458,366 shares available for future issuance under the 2013 Plan.

The 2013 Plan provides for an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2014 and continuing until the expiration of the 2013 Plan, equal to the lesser of (i) 2,000,000 shares of common stock, (ii) 4% of the outstanding shares of common stock on such date or (iii) an amount determined by our Board of Directors. On January 1, 2023, the annual increase for the 2013 Plan resulted in an additional 2,000,000 shares authorized for issuance.

Stock options

The following table summarizes the stock option activity of all stock incentive plans for the year ended December 31, 2022:

	Number of Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2021	4,798,826	$ 58.51	6.24	$ 4,697
Granted	1,850,093	28.89		
Exercised	(15,539)	11.50		
Forfeited/Expired	(860,816)	60.91		
Outstanding at December 31, 2022	5,772,564	$ 48.81	6.50	$ 5,362
Exercisable at December 31, 2022	3,497,660	$ 58.24	4.84	$ 3,141
Vested and expected to vest at December 31, 2022	5,772,564	$ 48.81	6.50	$ 5,362

The weighted-average grant date fair value of options granted was $15.64, $31.20 and $32.10 during the years ended December 31, 2022, 2021 and 2020, respectively. The total intrinsic value of options exercised was $0.3 million, $8.5 million and $10.4 million during the years ended December 31, 2022, 2021 and 2020, respectively.

At December 31, 2022, the total unrecognized compensation expense related to unvested stock option awards was $38.1 million, which we expect to recognize over a weighted-average period of approximately 2.71 years.

Restricted stock units

Upon vesting, each RSU entitles the holder to receive a specified number of shares of our common stock. The following table presents RSU activity for the year ended December 31, 2022:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2021	1,002,924	$ 51.51
Granted	869,766	31.16
Vested	(531,304)	50.16
Forfeited	(223,465)	41.84
Unvested shares at December 31, 2022	1,117,921	$ 38.30

As of December 31, 2022, there was approximately $25.6 million of total unrecognized compensation expense related to RSUs, which we expect to be recognized over a weighted-average period of 1.76 years.

Performance-based stock units

At the achievement of the performance-based and service-based vesting criteria, each PSU entitles the holder to receive a specified number of shares of our common stock. The following table presents PSU activity for the year ended December 31, 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	(47,190)		49.06
Expired	(40,092)		56.52
Unvested shares at December 31, 2022	430,243	$	35.87

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 December 31, 2022, there was no unrecognized compensation expense related to PSUs with performance-based vesting criteria that are considered probable of achievement that we expect to recognize. There is $15.4 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

We have issued certain equity awards that contain market based vesting conditions, in which shares of stock are earned at vesting based on stock price performance. 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.

The following table presents MSU activity for the year ended December 31, 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 December 31, 2022	42,695	$	41.50

As of December 31, 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. On January 1, 2023, the annual increase for the 2013 ESPP resulted in an additional 509,091 shares authorized for issuance. We issued 104,867 shares and 94,888 shares during the years ended December 31, 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 December 31, 2022, we had 1,289,780 shares available for future issuance under the 2013 ESPP.

Stock-based compensation expense

During the years ended December 31, 2022, 2021 and 2020, we recorded stock-based compensation expense for employee and non-employee stock options, RSUs, PSUs, ESPP shares and other stock-based awards. Stock-based compensation expense by award type included within the consolidated statements of operations is as follows:

(In thousands)	2022	2021	2020
Stock options	$ 23,731	$ 30,985	$ 37,705
Restricted stock units	21,670	21,510	19,893
Performance-based stock units	2,919	—	1,760
Employee Stock Purchase Plan	976	1,013	1,463
Other stock awards	—	—	781
Total stock-based compensation expense	$ 49,296	$ 53,508	$ 61,602

Expenses related to equity-based awards were allocated as follows in the consolidated statements of operations:

(In thousands)	2022	2021	2020
Research and development expense	$ 20,988	$ 24,527	$ 27,119
Selling, general and administrative expense	28,308	28,981	34,483
Total stock-based compensation expense	$ 49,296	$ 53,508	$ 61,602

No related tax benefits were recognized for the years ended December 31, 2022, 2021 and 2020.

The fair value of each stock option granted to employees and non-employees is estimated on the date of grant using the Black-Scholes option-pricing model. The following table summarizes the weighted average assumptions used in calculating the grant date fair value of the awards:

	2022	2021	2020
Risk-free interest rate	2.55 %	0.72 %	1.24 %
Expected dividend yield	—	—	—
Expected term (in years)	6.03	6.05	6.05
Expected volatility	55.30 %	61.72 %	73.80 %

Expected term

We use the “simplified method” as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, *Share Based Payments*, to estimate the expected term of stock option grants. Under this approach, the weighted-average expected life is presumed to be the average of the contractual term of ten years and the weighted-average vesting term of the stock options, taking into consideration multiple vesting tranches. We utilize this method due to lack of historical data and the plain-vanilla nature of our share-based awards.

Volatility

The expected volatility has been determined using Agios' historical volatilities for a period equal to the expected term of the option grant.

Risk-free rate

The risk-free rate is based on the yield curve of U.S. Treasury securities with periods commensurate with the expected term of the options being valued.

Dividends

We have never paid, and do not anticipate paying, any cash dividends in the foreseeable future, and, therefore, use an expected dividend yield of zero in the option-pricing model.

Forfeitures

We account for forfeitures as they occur and, therefore, do not estimate forfeitures.

Note 10. Net Income (Loss) per Share

Basic net income (loss) per share is calculated by dividing net income (loss) by the weighted-average shares outstanding during the period, without consideration for common stock equivalents. Diluted net income (loss) per share is calculated by adjusting 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 income (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 December 31, 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 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 (loss) from discontinued operations per share or net income (loss) per share. Basic and diluted net loss per share were 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:

	Years ended December 31,		
	2022	2021	2020
Stock options	5,772,564	4,798,826	6,143,046
Restricted stock units	1,117,921	1,002,924	1,284,378
Employee Stock Purchase Plan shares	42,026	39,864	46,439
Total	6,932,511	5,841,614	7,473,863

Note 11. Income Taxes

The domestic and foreign components of loss from continuing operations before income taxes are as follows:

(In thousands)	2022	2021	2020
Domestic	$ (231,767)	$ (356,665)	$ (330,669)
Foreign	(34)	155	1,364
Total	$ (231,801)	$ (356,510)	$ (329,305)

We did not have any material provision for income taxes for the years ended December 31, 2022, 2021 and 2020.

A reconciliation of the expected income tax benefit (expense) computed using the federal statutory income tax rate to our effective income tax rate is as follows for the years ended December 31, 2022, 2021 and 2020:

	2022	2021	2020
Income tax benefit computed at federal statutory tax rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal benefit	2.9 %	2.6 %	2.5 %
Change in valuation allowance	(25.7)%	(24.5)%	(28.2)%
General business credits and other credits	5.2 %	5.3 %	7.0 %
Permanent differences and other adjustments	(2.3)%	(3.9)%	(1.6)%
Stock based compensation	(1.1)%	(0.5)%	(0.7)%
Total	— %	— %	— %

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amount of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of our deferred tax assets and liabilities for the years ended December 31, 2022 and 2021 are as follows:

(In thousands)	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 32,907	$ 39,186
Tax credit carryforwards	163,780	152,128
Purchased intangible assets	11,583	12,150
Stock-based compensation	26,236	27,217
Operating lease liability	21,042	22,963
Non-deductible accruals and reserves, including inventory	3,992	4,033
Section 174 R&D expense	56,565	—
Total deferred tax assets	316,105	257,677
Depreciation and amortization	(3,767)	(3,168)
Operating lease right of use asset	(16,345)	(18,031)
Less: valuation allowance	(295,993)	(236,478)
Net deferred taxes	$ —	$ —

The Tax Cuts and Jobs Act (TCJA) requires taxpayers to capitalize and amortize research and experimental expenditures under section 174 for tax years beginning after December 31, 2021. This rule became effective for the Company during the year ending December 31, 2022 and resulted in the capitalization of research and development costs of $261.4 million. We will amortize these costs for tax purposes over 5 years if the research and development was performed in the U.S. and over 15 years if the research and development was performed outside the U.S.

As of December 31, 2022, we had net operating loss carryforwards, or NOLs, available to reduce state and foreign income taxes of approximately $1.2 billion and $65.2 million, respectively. At December 31, 2022, we also had available research and development tax credits for federal and state income tax purposes of approximately $16.9 million and $25.7 million, respectively. If not utilized, the credits begin to expire in 2039 and 2027 for federal and state income tax purposes, respectively. We engaged in clinical testing activities and incurred expenses that qualify for the federal orphan drug tax credit. At December 31, 2022, we had available orphan drug tax credits for federal purposes only of approximately $126.5 million. If not utilized, the orphan drug credits begin to expire in 2035.

As provided by Section 382 of the Internal Revenue Code of 1986, or Section 382, and similar state provisions, utilization of NOLs and tax credit carryforwards may be subject to substantial annual limitations due to ownership change limitations that have previously occurred or that could occur in the future. Ownership changes may limit the amount of NOLs and tax credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an ownership change, as defined by Section 382, results from transactions that increase the ownership of five percent stockholders in the stock of a corporation by more than 50 percent in the aggregate over a three year period. We completed a review of our changes in ownership through December 31, 2022 and determined that transactions have resulted in no ownership changes during the year ended December 31, 2022, as defined by Section 382. The impact of the historical ownership changes has been reflected in our deferred tax assets in the table above.

As required by ASC 740, we have evaluated the positive and negative evidence bearing upon the realizability of our deferred tax assets. Based on the weight of available evidence, both positive and negative, we recorded a valuation allowance of $296.0 million and $236.5 million as of December 31, 2022 and December 31, 2021, respectively, because we have determined that it is more likely than not that these assets will not be fully realized. The valuation allowance increased by $59.5 million for the year ended December 31, 2022 primarily due to the Section 174 R&D expense capitalization and decreased by $358.3 million for the year ended December 31, 2021 primarily due to the utilization of net operating losses and tax credits.

The following table presents our change in valuation allowance for the years ended December 31, 2022 and, 2021:

(in thousands)	2022	2021
Valuation allowance at the beginning of the year	$ 236,478	$ 594,752
Increase (decrease) for the current period	59,515	(358,274)
Valuation allowance at the end of the year	$ 295,993	$ 236,478

As of December 31, 2022, the unremitted earnings of our foreign subsidiaries are not material. We have not provided for U.S. income taxes or foreign withholding taxes on these earnings as it is our current intention to permanently reinvest these earnings outside the U.S. The tax liability on these earnings is also not material. Events that could trigger a tax liability include, but are not limited to, distributions, reorganizations or restructurings and/or tax law changes.

We apply the accounting guidance in ASC 740 related to accounting for uncertainty in income taxes. Our reserves related to taxes are based on a determination of whether, and how much of, a tax benefit taken by us in our tax filings or positions is more likely than not to be realized following resolution of any potential contingencies present related to the tax benefit.

The following table presents our unrecognized tax benefits activity for the years ended December 31, 2022 and 2021:

(In thousands)	2022	2021
Unrecognized tax benefits at the beginning of the year	$ 24,220	$ 21,131
Gross increases - current period tax positions	1,970	3,089
Unrecognized tax benefits at the end of the year	$ 26,190	$ 24,220

We will recognize interest and penalties related to uncertain tax positions above the line as an expense to continuing operations. As of December 31, 2022 and 2021, we had no accrued interest or penalties related to uncertain tax positions and no such amounts have been recognized. If all of the Company's unrecognized tax benefits as of December 31, 2022 were to become recognizable in the future, we would record $26.2 million of unrecognized tax benefits. The uncertain tax position does not impact our effective income tax rate due to the full valuation allowance.

We are subject to taxation in the United States, Switzerland, Netherlands, Germany, Italy and France. The statute of limitations for assessment by the IRS and state tax authorities is open for tax years ending December 31, 2022, 2021, 2020, and 2019, although carryforward attributes that were generated for tax years prior to 2019 may still be adjusted upon examination by the IRS or state tax authorities if they either have been, or will be, used in a future period. The statute of limitations for assessment in Switzerland remains open for tax years ending December 31, 2022, 2021, 2020, and 2019. The Company's subsidiaries in the Netherlands and Germany were incorporated in 2019 and therefore the statute of limitations for assessment that remain open in these jurisdictions are for the tax years ending December 31, 2022, 2021, 2020 and 2019. The Company's subsidiaries in Italy and France were incorporated in 2020 and therefore the statute of limitations for assessment that remain open in these jurisdictions are for the tax years ending December 31, 2022, 2021 and 2020. There are currently no federal, state or foreign audits in progress.

As of December 31, 2022 and 2021, we had an income tax receivable of $0.3 million and $2.9 million, respectively, recorded within prepaid expenses and other assets.

Note 12. Property and Equipment, net

Property and equipment, net consisted of the following at December 31:

(In thousands)	2022	2021
Laboratory equipment	$ 23,182	$ 22,165
Computer equipment and software	6,179	6,913
Leasehold improvements	37,277	32,726
Furniture and fixtures	3,514	3,035
Office equipment	2,248	1,690
Construction in progress	657	7,368
Total property and equipment	73,057	73,897
Less: accumulated depreciation	(50,070)	(44,974)
Total property and equipment, net	$ 22,987	$ 28,923

Depreciation expense for the years ended December 31, 2022, 2021 and 2020 was $8.4 million, $8.8 million and $9.4 million, respectively.

Note 13. Common Stock

We are authorized to issue 125,000,000 shares of our common stock. Holders of common stock are entitled to one vote per share. Additionally, holders of common stock are entitled to receive dividends, if and when declared by our board of directors, and to share ratably in our assets legally available for distribution to our shareholders in the event of liquidation.

Note 14. Share Repurchase Program

On March 25, 2021, we announced that our board of directors authorized the Repurchase Program for the repurchase of up to $1.2 billion of our outstanding shares of common stock. On March 31, 2021, in connection with the Repurchase Program, we entered into a definitive share repurchase agreement with BMS to repurchase 7.1 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 to which we may repurchase up to $600.0 million of shares of our common stock. As of December 31, 2022, we have 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. In total, as of December 31, 2022, we have repurchased 16.2 million shares of common stock for $802.5 million, or $49.49 per share, under the Repurchase Program.

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

Repurchased shares are held as treasury stock until they are retired or re-issued. Treasury stock purchases are accounted for under the cost method whereby the entire cost of the acquired stock is recorded as treasury stock. Repurchases of our common stock are accounted for as of the settlement date. There were no retirements or re-issuances of treasury stock during the year ended December 31, 2022.

Note 15. Discontinued Operations

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

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

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

The following table presents the gain on the sale for the year ended December 31, 2021:

(in thousands)		December 31, 2021
Cash proceeds	$	1,802,936
Less: transaction and insurance costs		(53,573)
Plus: net liabilities distributed, including working capital adjustment		239,770
Gain on sale, pre-tax		1,989,133
Income tax expense		(12,799)
Gain on sale, net of tax	$	1,976,334

As of December 31, 2022 and December 31, 2021, there were no assets or liabilities classified as discontinued operations.

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

(in thousands)	2021	2020
Revenues:		
Product revenue, net	$ 36,909	$ 121,089
Collaboration revenue – related party	1,350	68,274
Collaboration revenue – other	491	3,571
Royalty revenue – related party	2,659	10,262
Total revenue	41,409	203,196
Cost and expenses:		
Cost of sales	706	2,805
Research and development	41,564	146,659
Selling, general and administrative	8,551	33,965
Total cost and expenses	50,821	183,429
(Loss) income from discontinued operations	(9,412)	19,767
Non-cash interest expense for the sale of future revenue	(5,697)	(17,832)
Gain on the sale of the oncology business	1,989,133	—
Income from discontinued operations, pre-tax	1,974,024	1,935
Income tax expense	(12,799)	—
Net income from discontinued operations	$ 1,961,225	$ 1,935

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

We also entered into a Transition Services Agreement with Servier, through which we provided transitional services related to discovery, clinical development, technical operations, commercial and general and administrative related activities through March 31, 2022.

The milestone payment for approval of vorasidenib and royalty payments related to vorasidenib and TIBSOVO® represent contingent consideration. Contingent consideration has been accounted for as a gain contingency in accordance with ASC 450, *Contingencies*, and will be recognized in earnings in the period when realizable. As described in Note 1, *Nature of Business*, on October 27, 2022, we sold our rights to future contingent payments to entities affiliated with Sagard and recognized income of $127.9 million within the gain on sale of contingent payments line item in our consolidated statements of operations for the year ended December 31, 2022.

Note 16. Commitments and Contingent Liabilities

Manufacturing Commitments

We are party to various agreements with contract manufacturing organizations that we are not contractually able to terminate for convenience and avoid any and all future obligations to the vendors. Under such agreements, we are obligated to make certain minimum payments, with the exact amounts in the event of termination to be based on the timing of the termination and the exact terms of the agreement.

Legal Contingencies

From time to time, we may be involved in disputes and legal proceedings in the ordinary course of business. These proceedings may include allegations of infringement of intellectual property, employment or other matters. We do not have any ongoing legal proceedings that, based on our estimates, could have a material effect on our consolidated financial statements.

Note 17. Defined Contribution Benefit Plan

We sponsor a 401(k) retirement plan, in which substantially all of our full-time employees are eligible to participate. Participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. We will

make matching contributions equal to 100% of the employee's contributions, subject to a maximum of 4% of eligible compensation.

Certain identified information has been excluded from the exhibit because it is both (i) not material and (ii) is the type of information that the registrant treats as private or confidential. Double asterisks denote omissions.

PURCHASE AND SALE AGREEMENT

dated as of October 27, 2022

by and among

AGIOS PHARMACEUTICALS, INC.,

as SELLER

THE ENTITIES SET FORTH ON SCHEDULE 1.1,

as PURCHASERS

and

the PURCHASER'S REPRESENTATIVE named herein

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PURCHASE AND SALE AGREEMENT

This PURCHASE AND SALE AGREEMENT (this "Purchase and Sale Agreement") dated as of October 27, 2022 is by and among Agios Pharmaceuticals, Inc., a Delaware corporation and the Person defined as "Seller" in the Counterparty Agreement (the "Seller"), and the entities set forth in Schedule 1.1 hereto (each individually a "Purchaser", and collectively, the "Purchasers"), and Sagard Healthcare Royalty Partners, LP, a Cayman Islands exempt limited partnership, as representative for the Purchasers (in such capacity, "Purchaser's Representative").

W I T N E S E T H:

WHEREAS, the Seller has the right to receive Royalties (as defined below) under the Counterparty Agreement equal to five percent (5%) of Net Sales of the Earn-Out Product;

WHEREAS, the Seller desires to sell, contribute, assign, transfer, convey and grant to the Purchasers, and the Purchasers desire to purchase, acquire and accept from the Seller the Purchased Assets described herein, upon and subject to the terms and conditions set forth in this Purchase and Sale Agreement;

NOW, THEREFORE, in consideration of the premises and the mutual agreements, representations and warranties set forth herein and of other good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, the parties hereto covenant and agree as follows:

ARTICLE 1
DEFINED TERMS AND RULES OF CONSTRUCTION

Defined Terms. The following terms, as used herein, shall have the following respective meanings:

"Acquisition Proposal" has the meaning set forth in the Counterparty Agreement.

"Affiliate" means, with respect to any Person, any other Person that, directly or indirectly, controls, is controlled by or is under common control with such Person. For purposes of this definition, "control" of a Person means the possession, directly or indirectly, of the power to direct or cause the direction of the management and policies of such Person, whether through the ownership of Voting Securities, by contract or otherwise, and the terms "controlled" and "controlling" have meanings correlative to the foregoing.

"Annual Net Sales Statement" has the meaning set forth in Section 2.13(a)(iv) of the Counterparty Agreement.

"Applicable Law" means, with respect to any Person, all laws, rules, regulations and orders of Governmental Authorities applicable to such Person or any of its properties or assets.

"Applicable Patent Rights" means the "Earn-Out Patent Rights" with respect to the Earn-Out Product described in sub-part (a) of the definition of "Earn-Out Patent Rights" in Section 1.1 of the Counterparty Agreement.

"Audit Reports" means any reports, summaries of preliminary conclusions, and final conclusions of any Independent Accounting Firm pursuant to Section 2.13(e) of the Counterparty Agreement.

"Bankruptcy Event" means the occurrence of any of the following in respect of a Person: (a) an admission in writing by such Person of its inability to pay its debts generally or a general assignment by such Person for the benefit of creditors; (b) the filing of any petition or answer by such Person seeking to adjudicate itself as bankrupt or insolvent, or seeking for itself any liquidation, winding-up, reorganization, arrangement, adjustment, protection, relief or composition of such Person or its debts under any Applicable Law relating to bankruptcy, insolvency, receivership, winding-up, liquidation, reorganization, examination, relief of debtors or other similar Applicable Law now or hereafter in effect, or seeking, consenting to or acquiescing in the entry of an order for relief in any case under any such Applicable Law, or the appointment of or taking possession by a receiver, trustee, custodian, liquidator, examiner, assignee, sequestrator or other similar official for such Person or for any substantial part of its property; (c) corporate or other entity action taken by such Person to authorize any of the actions set forth in clause (a) or clause (b) above; or (d) without the consent or acquiescence of such Person, the entering of an order for relief or approving a petition for relief or reorganization or any other petition seeking any reorganization, arrangement, composition, readjustment, liquidation, dissolution or other similar relief under any present or future bankruptcy, insolvency or similar Applicable Law, or the filing of any such petition against such Person, or, without the consent or acquiescence of such Person, the entering of an order appointing a trustee, custodian, receiver or liquidator of such Person or of all or any substantial part of the property of such Person, in each case where such petition or order shall remain unstayed or shall not have been stayed or dismissed within 90 days from entry thereof.

"Bill of Sale" means that certain bill of sale effective as of the Effective Date executed by the Seller and each of the Purchasers substantially in the form of Exhibit A.

"Business Day" means any day that is not a Saturday, Sunday or other day on which commercial banks in New York City are authorized or required by Applicable Law to remain closed.

"Capital Securities" means, with respect to any Person, all shares, interests, participations or other equivalents (however designated, whether voting or non-voting) of such Person's capital, whether now outstanding or issued after the Effective Date, including common shares, ordinary shares, preferred shares, membership interests or share capital in a limited liability company or other Person, limited or general partnership interests in a partnership, beneficial interests in trusts or any other equivalent of such ownership interest or any options, warrants and other rights to acquire such shares or interests, including rights to allocations and distributions, dividends, redemption payments and liquidation payments.

"Code" means the U.S. Internal Revenue Code of 1986, as amended, and the regulations thereunder.

"Competitor" means [**].

"Counterparty" means each of Servier and Servier SAS, and their permitted successors and assigns (collectively, the "Counterparties").

"Counterparty Agreement" means that certain Purchase and Sale Agreement, dated as of December 20, 2020, by and among Seller and the Counterparties, as amended, modified or otherwise supplemented from time to time, including pursuant to the Counterparty Consent.

"Counterparty Consent" means that certain Consent Agreement dated July 28, 2022 between Seller and Counterparty, a true, correct and complete copy of which is attached hereto as Exhibit F.

"Counterparty Instruction" means the irrevocable direction to each Counterparty in the form set forth in Exhibit B.

"Credit Event" means any insolvency, bankruptcy, receivership, assignment for the benefit of creditors, or similar proceeding, following or as a result of which the Counterparties fail to pay amounts owing under the Counterparty Agreement in respect of the Royalties as a result of the Counterparties' financial distress, creditworthiness, or insolvency.

"Deposit Account" means the bank account described on the Schedule 1.2 under the heading "Deposit Account" for the benefit of the Purchasers, as such bank account may be changed by Purchaser's Representative in its sole discretion from time to time upon prior written notice to the Seller in accordance with Section 5.4(b).

"Disclosure Schedule" means the Disclosure Schedule, attached hereto as Exhibit E and dated as of the date hereof and delivered by the Seller to each of the Purchasers.

"Disputed Amount" has the meaning set forth in Section 2.13(j) of the Counterparty Agreement.

"Dollar" or the sign "$" means United States dollars.

"Earn-Out Product" means any product containing or comprising ivosidenib, NDC 71334-100.

"Earn-Out Product Transaction" has the meaning set forth in Section 2.13(g) of the Counterparty Agreement.

"Effective Date" means the date of this Agreement.

"ERISA" means the U.S. Employee Retirement Income Security Act of 1974, as amended, and the regulations thereunder.

"Excluded Liabilities and Obligations" has the meaning set forth in Section 2.3.

"FD&C Act" means the United States Federal Food, Drug, and Cosmetic Act.

"FDA" means the U.S. Food and Drug Administration, or any successor agency thereto.

"GAAP" means generally accepted accounting principles in effect in the United States from time to time.

"Governmental Authority" means the government of the United States, any other nation or any political subdivision thereof, whether state or local, and any agency, authority (including supranational authority), commission, instrumentality, regulatory body, court, central bank or other Person exercising executive, legislative, judicial, taxing, regulatory or administrative powers or functions of or pertaining to government.

"Independent Accounting Firm" has the meaning set forth in the Counterparty Agreement.

"Knowledge" means, with respect to the Seller, the actual knowledge of [**], or any successor to any such individuals holding the same or substantially similar officer positions at

the applicable time, after internal due inquiry with such individuals (and excluding, for the avoidance of doubt, any inquiries with the Counterparty or any other third party).

"Lien" means any security interest, mortgage, pledge, hypothecation, assignment, deposit arrangement, encumbrance, lien (statutory or otherwise), charge against or interest in property or other priority or preferential arrangement of any kind or nature whatsoever, in each case to secure payment of a debt or performance of an obligation, including any conditional sale or any sale with recourse, or any other restriction on transfer.

"Loss" means any loss, damage, assessment, award, cause of action, claim, charge, cost, expense, fine, judgment, liability, obligation, penalty or Royalty Reduction for which, in the case of any Royalty Reduction, Seller is liable under Section 5.4(c) and as to which Seller has not paid Purchaser in accordance with Section 5.4(c).

"Majority Purchasers" means Purchasers who hold, in the aggregate, at least 50.1% of the Specified Percentage.

"Material Adverse Change" means (i) a material adverse effect on the legality, validity or enforceability of the Transaction Documents or the Counterparty Agreement (as it relates to the Purchased Assets), (ii) a material adverse effect on the ability of the Seller to perform any of its obligations under the Transaction Documents, (iii) a material adverse effect on the rights of the Seller or Purchasers under the Counterparty Agreement with respect to the Purchased Assets, other than as a result of a Permitted Deduction or Credit Event, (iv) a material adverse effect on the validity or enforceability of any of the Applicable Patent Rights that, if adversely determined, would reasonably be expected to adversely affect in any material respect the timing, amount or duration of the payments to be made to the Purchasers in respect of the Purchased Assets, or (v) an adverse effect in any material respect on the timing, amount or duration of the payments to be made to the Purchasers in respect of the Royalties or the right of the Purchasers to receive such payments, other than as a result of a Permitted Deduction or Credit Event.

"Net Sales" has the meaning set forth in Section 1.1 of the Counterparty Agreement.

"Net Sales Statement" has the meaning set forth in Section 1.1 of the Counterparty Agreement.

"Net Sales Term" has the meaning set forth in Section 1.1 of the Counterparty Agreement as it relates to the Earn-Out Product.

"Permitted Deductions" means (i) the deductions set forth in items (a)-(k) of the definition of "Permitted Deductions" in Section 1.1 of the Counterparty Agreement to the extent such deductions are actually taken by the Counterparty in the calculation of "Net Sales" for sales of the Earn-Out Product that are made in the US Territory from and after July 1, 2022, (ii) offsets permitted under clause (B) of the second sentence of 2.13(a)(iv) and Section 2.13(e)(B) of the Counterparty Agreement resulting from Counterparty overpayment of Royalties to Purchasers, in each case in respect of "Net Sales" of the Earn-Out Product made in the US Territory from and after July 1, 2022, and (iii) any deductions or withholdings for Taxes required under Applicable Law in accordance with and subject to Section 5.7(b). For the avoidance of doubt, no other right of set-off, off-set, counterclaim, deduction, withholding, or credit, by contract or otherwise (including offsets or reductions in respect of Third Party License Payments pursuant to Section 2.13(a)(ii) of the Counterparty Agreement and any offsets or reductions taken on account of any Disputed Amounts under Section 2.13(j) of the Counterparty Agreement) are Permitted Deductions.

"Person" means any natural person, firm, corporation, limited liability company, partnership, joint venture, association, joint-stock company, trust, unincorporated organization, Governmental Authority or any other legal entity, including public bodies, whether acting in an individual, fiduciary or other capacity.

"Plan" means an employee benefit plan subject to Title 1 of ERISA, an individual retirement account or annuity subject to Section 4975 of the Code or any other employee benefit plan (within the meaning of Section 3(3) of ERISA), whether or not subject to ERISA.

"Purchase and Sale Agreement" has the meaning set forth in the preamble.

"Purchase Price" has the meaning set forth in Section 2.2.

"Purchased Assets" means, collectively, (a) the Seller's right, title and interest in, to and under the Counterparty Agreement with respect to the Royalties and the Royalty Reports, and (b) the right to transfer, assign or pledge the foregoing, in whole or in part, and the payments, accounts, proceeds and income of, and the rights to enforce, each of the foregoing. The Purchased Assets do not include any other rights under the Counterparty Agreement or otherwise.

"Purchaser Indemnified Party" has the meaning set forth in Section 7.1.

"Purchasers" has the meaning set forth in the preamble.

"Purchaser's Representative" has the meaning set forth in the preamble.

"Qualified Assignee" means: (i) [**]; or (ii) any other Person designated as such in writing by mutual agreement of the Seller and the Majority Purchasers.

"Quarterly Net Sales Statement" has the meaning set forth in Section 2.13(a)(iii) of the Counterparty Agreement.

"Regulatory Agency" means a Governmental Authority with responsibility for the approval of the marketing and sale of pharmaceuticals or other regulation of pharmaceuticals in any jurisdiction.

"Regulatory Approvals" mean, collectively, all regulatory approvals, registrations, certificates, authorizations, permits and supplements thereto, as well as associated materials (including the product dossier) pursuant to which the Earn-Out Product may be marketed, sold and distributed in a jurisdiction, issued by the appropriate Regulatory Agency.

"Royalties" means (a) 100% of all amounts or fees due, paid or payable, owed or owing, accrued or otherwise to be paid to the Seller or any of its Affiliates under Section 2.13(a)(i)(A) of the Counterparty Agreement in respect of aggregate annual Net Sales of the Earn-Out Product made in the US Territory from and after July 1, 2022 during the Net Sales Term, and any amounts in lieu thereof, but in each case without giving effect to any offsets or reductions in respect of Third Party License Payments pursuant to Section 2.13(a)(ii) of the Counterparty Agreement or any offsets or reductions taken on account of any Disputed Amounts under Section 2.13(j) of the Counterparty Agreement, (b) all amounts payable resulting from Counterparty underpayments in respect of Net Sales of the Earn-Out Product made in the US Territory from and after July 1, 2022 pursuant to (i) Section 2.13(a)(iii)(B) of the Counterparty Agreement, (ii) clause (B) of the first sentence in Section 2.13(a)(iv) of the Counterparty Agreement, and (iii) Section 2.13(e) of the Counterparty Agreement (in each case (b)(i)-(b)(iii) above, regardless of

whether Seller furnishes an invoice to Counterparty for such amounts), (c) all indemnity payments, guarantees, recoveries, damages or awards or settlement amounts paid or payable to the Seller or any of its Affiliates as a result of a breach by either Counterparty of the provisions of the Counterparty Agreement related to the Purchased Assets in respect of the amounts described in clause (a) and (b) above, including pursuant to Section 10.3, Section 10.5, and Section 11.15 of the Counterparty Agreement (other than for any unreimbursed costs payable to Seller pursuant to the Counterparty Agreement), (d) any payments payable to Seller under Section 2.13(i) of the Counterparty Agreement in respect of the payments described in clauses (a)-(c) above, (e) all other amounts paid or payable by Counterparty or any other Person to the Seller or any of its Affiliates arising out of, related to or resulting from the amounts described in clauses (a), (b), (c) and (d) above, (f) all accounts (as defined under the UCC) evidencing the rights to the payments and amounts described in clauses (a)-(e) above, and (g) all proceeds (as defined under the UCC) of any of the foregoing.

"Royalty Reduction" means any right of set-off, off-set, counterclaim, deduction, withholding, or credit, by contract or otherwise, including pursuant to Section 2.13(a)(ii) or Section 2.13(j) of the Counterparty Agreement, other than any Permitted Deductions.

"Royalty Reports" mean Seller's right to: (i) receive the Quarterly Net Sales Statements produced by Counterparty pursuant to Section 2.13(a)(iii) of the Counterparty Agreement in respect of Net Sales of the Earn-Out Product, (ii) receive the Annual Net Sales Statements produced by Counterparty pursuant to Section 2.13(a)(iv) of the Counterparty Agreement in respect of Net Sales of Earn-Out Product, and (iii) receive a summary of preliminary conclusions of any Independent Accounting Firm and to provide comments thereon pursuant to Section 2.13(e) of the Counterparty Agreement and receive the final conclusions of such Independent Accounting Firm pursuant to Section 2.13(e) of the Counterparty Agreement

"Sale Date" means the "Closing Date" as defined in the Counterparty Agreement, which was March 31, 2021.

"Seller" has the meaning set forth in the preamble.

"Seller Account" means the account described on Schedule 1.2 (or to such other account as the Seller shall notify, the Purchaser in writing from time to time).

"Seller Indemnified Party" has the meaning set forth in Section 7.2.

"Servier" means Servier Pharmaceuticals, LLC, a Delaware limited liability company and the Person defined as "Purchaser" in the Counterparty Agreement.

"Servier SAS" means Servier S.A.S., a French *societe par actions simplifiee* and the Person defined as "Purchaser Guarantor" in the Counterparty Agreement.

"Specified Indemnity Claim" has the meaning set forth in Section 2.13(j) of the Counterparty Agreement.

"Specified Percentage" means, with respect to a Purchaser as of any date of determination, the "Specified Percentage" set forth in Schedule 1.1 with respect to such Purchaser (as may be amended by the Purchasers from time to time to reflect assignments permitted by Section 8.4).

"Specified Purchase Price" means, with respect to each Purchaser, the "Specified Purchase Price" set forth in Schedule 1.1 with respect to such Purchaser.

"Specified Tax Withholding" has the meaning set forth in Section 5.7(b).

"Sublicensee" means any licensee or sublicensee of Counterparty in respect of the Earn-Out Products.

"Subsidiary" means, with respect to any Person, any other Person of which more than 50% of the outstanding Voting Securities of such other Person (irrespective of whether at the time Capital Securities of any other class or classes of such other Person shall or might have voting power upon the occurrence of any contingency) is at the time directly or indirectly owned or controlled by such Person, by such Person and one or more other Subsidiaries of such Person or by one or more other Subsidiaries of such Person.

"Tax" or "Taxes" means any federal, state, local or foreign income, gross receipts, license, payroll, employment, excise, severance, occupation, premium, windfall profits, environmental, customs duties, capital stock, franchise, profits, withholding, social security, unemployment, disability, real property, personal property, abandoned property, value added, alternative or add-on minimum, estimated or other tax of any kind whatsoever, including any interest, penalty or addition thereto, whether disputed or not.

"Third Party License Payments" has the meaning set forth in Section 1.1 of the Counterparty Agreement.

"Transaction Documents" means this Purchase and Sale Agreement, the Bill of Sale and the Counterparty Instruction.

"UCC" means the Uniform Commercial Code as in effect from time to time in the State of Delaware; provided, that, if, with respect to any financing statement or by reason of any provisions of Applicable Law, the perfection or the effect of perfection or non-perfection of the backup security interest or any portion thereof granted pursuant to Section 2.1(e) is governed by the Uniform Commercial Code as in effect in a jurisdiction of the United States other than the State of Delaware, then "UCC" means the Uniform Commercial Code as in effect from time to time in such other jurisdiction for purposes of the provisions of this Purchase and Sale Agreement and any financing statement relating to such perfection or effect of perfection or non-perfection.

"U.S." or "United States" means the United States of America, its 50 states, each territory thereof and the District of Columbia.

"US Territory" has the meaning set forth in Section 1.1 of the Counterparty Agreement.

"Voting Securities" means, with respect to any Person, Capital Securities of any class or kind ordinarily having the power to vote for the election of directors, managers or other voting members of the governing body of such Person.

Section 1.1 Rules of Construction. Unless the context otherwise requires, in this Purchase and Sale Agreement:

a. A term has the meaning assigned to it and an accounting term not otherwise defined has the meaning assigned to it in accordance with GAAP.

b. Unless otherwise defined, all terms that are defined in the UCC shall have the meanings stated in the UCC.

c. Words of the masculine, feminine or neuter gender shall mean and include the correlative words of other genders.

d. The definitions of terms shall apply equally to the singular and plural forms of the terms defined.

e. The terms “include”, “including” and similar terms shall be construed as if followed by the phrase “without limitation”.

f. Unless otherwise specified, references to an agreement or other document include references to such agreement or document as from time to time amended, restated, reformed, supplemented or otherwise modified in accordance with the terms thereof (subject to any restrictions on such amendments, restatements, reformations, supplements or modifications set forth herein) and include any annexes, exhibits and schedules attached thereto.

g. References to any Applicable Law shall include such Applicable Law as from time to time in effect, including any amendment, modification, codification, replacement or reenactment thereof or any substitution therefor.

h. References to any Person shall be construed to include such Person’s successors and permitted assigns (subject to any restrictions on assignment, transfer or delegation set forth herein or in any of the other Transaction Documents), and any reference to a Person in a particular capacity excludes such Person in other capacities.

i. The word “will” shall be construed to have the same meaning and effect as the word “shall”.

j. The words “hereof”, “herein”, “hereunder” and similar terms when used in this Purchase and Sale Agreement shall refer to this Purchase and Sale Agreement as a whole and not to any particular provision hereof, and Article, Section and Exhibit references herein are references to Articles and Sections of, and Exhibits to, this Purchase and Sale Agreement unless otherwise specified.

k. In the computation of a period of time from a specified date to a later specified date, the word “from” means from and including, and each of the words “to” and “until” means “to but excluding”.

l. Any interpretation of whether an action or consent (or refusal to act or consent) or any instruction by any Purchaser or the Seller is “reasonable,” shall take into the account the relative economic interests of the Seller, on the one hand, and such Purchaser, on the other, in the reasonably expected future amounts due, paid or payable, owed or owing, accrued or otherwise to be paid by Counterparty or any of its Affiliates under Section 2.13(a)(i)(A) of the Counterparty Agreement in respect of Net Sales of Earn-Out Products.

m. Where any payment is to be made, any funds are to be applied or any calculation is to be made under this Purchase and Sale Agreement on a day that is not a Business Day, unless this Purchase and Sale Agreement otherwise provides, such payment shall be made, such funds shall be applied and such calculation shall be made on the succeeding Business Day, and payments shall be adjusted accordingly.

n. Any reference herein to a term that is defined by reference to its meaning in the Counterparty Agreement shall refer to such term’s meaning in the Counterparty Agreement as in existence on the date hereof and provided to the Purchasers as set forth in

Section 3.14(b) (and not to any new, substituted, amended, modified or supplemented version thereof unless the Purchasers have consented thereto in writing).

ARTICLE 2
PURCHASE AND SALE OF THE PURCHASED ASSETS

Section 2.1 Purchase and Sale.

a. Subject to the terms and conditions of this Purchase and Sale Agreement, the Seller hereby sells, contributes, assigns, transfers, conveys and grants to each Purchaser, and each Purchaser hereby purchases, acquires and accepts from the Seller, such Purchaser's Specified Percentage of all of the Seller's rights, title and interest in and to the Purchased Assets, free and clear of any and all Liens, other than those Liens created in favor of such Purchaser by Sections 2.1(e) hereof.

b. The Seller and the Purchasers intend and agree that the sale, contribution, assignment, transfer, conveyance and granting of the Purchased Assets under this Purchase and Sale Agreement shall be, and are, a true, complete, absolute and irrevocable assignment and sale by the Seller to the Purchasers of the Purchased Assets and that such assignment and sale shall provide the Purchasers (or their respective permitted assigns) with the full benefits of ownership of the Purchased Assets. Neither the Seller nor the Purchasers intend the transactions contemplated hereby to be, or for any purpose characterized as, a loan from the Purchasers to the Seller or a pledge or assignment or a security agreement. The Seller waives any right to contest or otherwise assert that this Purchase and Sale Agreement does not constitute a true, complete, absolute and irrevocable sale and assignment by the Seller to the Purchasers of the Purchased Assets under Applicable Law, which waiver shall be enforceable against the Seller in any Bankruptcy Event in respect of the Seller. The sale, contribution, assignment, transfer, conveyance and granting of the Purchased Assets shall be reflected on the Seller's financial statements and other records as a sale of assets to the Purchasers (except to the extent GAAP require otherwise with respect to the Seller's consolidated financial statements).

c. The Seller hereby authorizes Purchaser's Representative or its designee to execute, record and file, and consents to Purchaser's Representative or its designee executing, recording and filing, at each Purchaser's sole cost and expense, financing statement, in the forms attached as Exhibit G, in the appropriate filing offices under the UCC (and continuation statements with respect to such financing statements or other amendments deemed necessary by Purchaser's Representative, if and when applicable) naming Purchaser's Representative, for the benefit of the Purchasers, as Secured Party thereunder, and amendments thereto or assignments thereof, in such manner and in such jurisdictions as are necessary or appropriate to evidence or perfect the sale, contribution, assignment, transfer, conveyance and grant by the Seller to the Purchasers, and the purchase, acquisition and acceptance by the Purchasers from the Seller, of the Purchased Assets and to perfect the security interest in the Purchased Assets granted by the Seller to Purchaser's Representative, for the benefit of the Purchasers pursuant to Section 2.1(e).

d. Each Purchaser's right, title and interest to the Purchased Assets shall commence as of the Effective Date.

e. Notwithstanding that the Seller and the Purchasers expressly intend for the sale, contribution, assignment, transfer, conveyance and granting of the Purchased Assets to be a true, complete, absolute and irrevocable sale and assignment, the Seller hereby assigns, conveys, grants and pledges to the Purchaser's Representative, for the benefit of the Purchasers, as security for its obligations created hereunder in the event that the transfer contemplated by this Purchase and Sale Agreement is held not to be a sale, a first priority security interest in and to

each Purchaser's Specified Percentage of all of the Seller's right, title and interest in, to and under the Purchased Assets, and, in such event, this Purchase and Sale Agreement shall constitute a security agreement.

Section 2.2 Purchase Price. In full consideration for the sale, contribution, assignment, transfer, conveyance and granting of the Purchased Assets, and subject to the terms and conditions set forth herein, on the Effective Date, each Purchaser shall pay (or cause to be paid) to the Seller, severally but not jointly, the sum set forth opposite such Purchaser's name on Schedule 1.1 attached hereto in the column entitled "Specified Purchase Price" for a total purchase price of $131,783,241.00 (the "Purchase Price") in immediately available funds by wire transfer to the Seller Account. Following the date of this Purchase and Sale Agreement, the parties hereto shall, acting reasonably, agree to an allocation of the Purchase Price among the Purchased Assets and memorialize this allocation in a separate writing. The parties hereto agree not to take any position that is inconsistent with the allocation set forth in such writing on any Tax return or in any audit or other Tax-related administrative or judicial proceeding, unless taking such a position is required by Applicable Law.

Section 2.3 No Assumed Liabilities or Obligations. Notwithstanding any provision in this Purchase and Sale Agreement to the contrary, each Purchaser is purchasing, acquiring and accepting only its Specified Percentage of the Purchased Assets and is not assuming any liability or obligation of the Seller or any of the Seller's Affiliates of whatever nature, whether presently in existence or arising or asserted hereafter (including any liability or obligation of the Seller under the Counterparty Agreement or otherwise). All such liabilities and obligations shall be retained by and remain liabilities and obligations of the Seller or the Seller's Affiliates, as the case may be (the "Excluded Liabilities and Obligations").

Section 2.4 Excluded Assets. The Purchasers do not, by purchase, acquisition or acceptance of the rights, title or interest granted hereunder or otherwise pursuant to any of the Transaction Documents, purchase, acquire or accept any assets or contract rights of the Seller under the Counterparty Agreement, other than the Purchased Assets, or any other assets of the Seller.

Section 2.5 Royalty Reports. Effective immediately upon the sale of the Purchased Assets hereunder and payment of the Purchase Price, the Purchaser shall have the right to receive the Royalty Reports pursuant to the Counterparty Agreement in accordance with the Counterparty Consent.

ARTICLE 3

REPRESENTATIONS AND WARRANTIES OF THE SELLER

The Seller hereby represents and warrants to the Purchasers on the Effective Date that:

Section 3.1 Organization. The Seller is a corporation duly organized, validly existing and in good standing under the laws of the State of Delaware and has all powers and authority, and all licenses, permits, franchises, authorizations, consents and approvals of all Governmental Authorities, required to own its property and conduct its business as now conducted and to exercise its rights and to perform its obligations under the Counterparty Agreement. The Seller is duly qualified to transact business and is in good standing in every jurisdiction in which such qualification or good standing is required by Applicable Law (except where the failure to be so qualified or in good standing would not be a Material Adverse Change). No Purchaser nor any of its partners, members or controlling Persons is an Affiliate of the Seller of any Subsidiary of the Seller.

Section 3.2 No Conflicts.

a. None of the execution and delivery by the Seller of any of the Transaction Documents to which the Seller is party, the performance by the Seller of the obligations contemplated hereby or thereby or the consummation of the transactions contemplated hereby or thereby will: (i) contravene, conflict with, result in a breach, violation, cancellation, termination of or loss of benefit under, constitute a default (with or without notice or lapse of time, or both) under, require prepayment under, give any Person the right to exercise any remedy or obtain any additional rights under, or accelerate the maturity or performance of or payment under, in any respect, (A) any Applicable Law or any judgment, order, writ, decree, permit or license of any Governmental Authority, to which the Seller or any of its Subsidiaries or any of their respective assets or properties may be subject or bound, (B) any term or provision of any contract, agreement, indenture, lease, license, deed, commitment, obligation or instrument to which the Seller or any of its Subsidiaries is a party or by which the Seller or any of its Subsidiaries or any of their respective assets or properties is bound or committed (including the Counterparty Agreement, after giving effect to the Counterparty Consent) to the extent it would reasonably be expected to result in a Material Adverse Change or (C) any term or provision of any of the organizational documents of the Seller or any of its Subsidiaries; (ii) give rise to any additional right of termination, cancellation or acceleration of any right or obligation of the Seller or any of its Subsidiaries to the extent it would reasonably be expected to result in a Material Adverse Change; or (iii) except as provided in any of the Transaction Documents to which it is party, result in or require the creation or imposition of any Lien on the Earn-Out Product, the Counterparty Agreement or the Purchased Assets.

b. Except for the Lien created in favor of Purchasers under Section 2.1(e) of this Purchase and Sale Agreement, the Seller has not granted, nor does there exist, any Lien on or relating to the Counterparty Agreement or the Purchased Assets.

Section 3.3 Authorization. The Seller has all powers and authority to execute and deliver, and perform its obligations under, the Transaction Documents to which it is party and to consummate the transactions contemplated hereby and thereby. The execution and delivery of each of the Transaction Documents to which the Seller is party and the performance by the Seller of its obligations hereunder and thereunder have been duly authorized by all necessary corporate action on the part of the Seller. Each of the Transaction Documents to which the Seller is party has been duly executed and delivered by an authorized officer of the Seller. Each of the Transaction Documents to which the Seller is party constitutes the legal, valid and binding obligation of the Seller, enforceable against the Seller in accordance with its respective terms, subject to applicable bankruptcy, insolvency, reorganization, moratorium or similar Applicable Laws affecting creditors' rights generally and general equitable principles.

Section 3.4 Ownership. The Seller is the exclusive owner of the entire right, title (legal and equitable) and interest in, to and under the Purchased Assets and has good, valid and marketable title thereto, free and clear of all Liens, other than Liens created in favor of the Purchasers under Section 2.1(e) of this Purchase and Sale Agreement. The Purchased Assets sold, contributed, assigned, transferred, conveyed and granted to the Purchasers on the Effective Date have not been pledged, sold, contributed, assigned, transferred, conveyed or granted by the Seller to any other Person. The Seller has full right to sell, contribute, assign, transfer, convey and grant the Purchased Assets to the Purchasers. Upon the sale, contribution, assignment, transfer, conveyance and granting by the Seller of the Purchased Assets to the Purchasers, the Purchasers shall acquire good and marketable title to the Purchased Assets free and clear of all Liens, other than Liens created in favor of the Purchasers under Section 2.1(e) of this Purchase and Sale Agreement, and shall be the exclusive owner of the Purchased Assets. The Purchasers

shall have the same rights as the Seller would have with respect to the Purchased Assets (if the Seller were still the owner of such Purchased Assets) against any other Person.

Section 3.5 Governmental and Third Party Authorizations. The execution and delivery by the Seller of the Transaction Documents to which the Seller is party, the performance by the Seller of its obligations hereunder and thereunder and the consummation of any of the transactions contemplated hereunder and thereunder (including the sale, contribution, assignment, transfer, conveyance and granting of the Purchased Assets to the Purchasers) do not require any consent, approval, license, order, authorization or declaration from, notice to, action or registration by or filing with any Governmental Authority or any other Person, except for the filing of UCC financing statements, the notice to the Counterparties contained in the Counterparty Instruction and any such consent, approval, license, order, authorization or declaration, notice, action or registration the failure of which to obtain would not reasonably be expected to result in a Material Adverse Change.

Section 3.6 No Litigation. There is no (a) action, suit, arbitration proceeding, claim, demand, citation, summons, subpoena, investigation or other proceeding (whether civil, criminal, administrative, regulatory, investigative or informal) pending or, to the Knowledge of the Seller, threatened against the Seller or any of its Subsidiaries, relating to the Counterparty, the Earn-Out Product or the Purchased Assets (including the Counterparty Agreement), at law or in equity, or (b) inquiry or investigation (whether civil, criminal, administrative, regulatory, investigative or informal) by or before a Governmental Authority pending or, to the Knowledge of the Seller, threatened against the Seller or any of its Subsidiaries relating to the Counterparty, the Counterparty Agreement, the Earn-Out Products or the Purchased Assets, that, in each case, (i) if adversely determined, could reasonably be expected to result in a Material Adverse Change, or (ii) challenges or seeks to prevent or delay the consummation of any of the transactions contemplated by any of the Transaction Documents to which the Seller is party. To the Knowledge of the Seller, no event has occurred or circumstance exists that may give rise to or serve as a basis for the commencement of any such action, suit, arbitration, claim, investigation, proceeding or inquiry.

Section 3.7 Solvency. The Seller has determined that, and by virtue of its entering into the transactions contemplated by the Transaction Documents to which the Seller is party and its authorization, execution and delivery of the Transaction Documents to which the Seller is party, the Seller's incurrence of any liability hereunder or thereunder or contemplated hereby or thereby is in its own best interests. Upon consummation of the transactions contemplated by the Transaction Documents and the application of the proceeds therefrom, (a) the fair saleable value of the Seller's assets will be greater than the sum of its debts, liabilities and other obligations, including contingent liabilities, (b) the present fair saleable value of the Seller's assets will be greater than the amount that would be required to pay its probable liabilities on its existing debts, liabilities and other obligations, including contingent liabilities, as they become absolute and matured, (c) the Seller will be able to realize upon its assets and pay its debts, liabilities and other obligations, including contingent obligations, as they mature, (d) the Seller will not be rendered insolvent, will not have unreasonably small capital with which to engage in its business and will not be unable to pay its debts as they mature, (e) the Seller has not incurred, will not incur and does not have any present plans or intentions to incur debts or other obligations or liabilities beyond its ability to pay such debts or other obligations or liabilities as they become absolute and matured, (f) the Seller will not have become subject to any Bankruptcy Event and (g) the Seller will not have been rendered insolvent within the meaning of Section 101(32) of Title 11 of the United States Code. No step has been taken or is intended by the Seller or, so far as it is aware, any other Person to make the Seller subject to a Bankruptcy Event.

Section 3.8 Tax Matters. No deduction or withholding for or on account of any Tax has been made, or was required under Applicable Law to be made, from any payment to the Seller under the Counterparty Agreement. Seller has received no notice from any Counterparty pursuant to the Counterparty Agreement of any intention to deduct or withhold any tax from any future payments to the Seller with respect to the Counterparty Agreement. The Seller has filed (or caused to be filed) all income and other material tax returns and reports required by Applicable Law to have been filed by it with respect to the Purchased Assets, and all such tax returns were true, correct and complete in all material respects, and the Seller has paid (or caused to be paid) all taxes required to be paid by it with respect to the Purchased Assets. There are no existing Liens for Taxes on the Purchased Assets (or any portion thereof) other than Liens for Taxes not yet due and payable.

Section 3.9 No Brokers' Fees. The Seller has not taken any action that would entitle any person or entity to any commission or broker's fee in connection with the transactions contemplated by this Purchase and Sale Agreement.

Section 3.10 [Reserved].

Section 3.11 Compliance with Laws. None of the Seller or any of its Subsidiaries (a) has violated or is in violation of, or, to the Knowledge of the Seller, is under investigation with respect to or has been threatened to be charged with or been given notice of any violation of, any Applicable Law or any judgment, order, writ, decree, injunction, stipulation, consent order, permit or license granted, issued or entered by any Governmental Authority or (b) is subject to any judgment, order, writ, decree, injunction, stipulation, consent order, permit or license granted, issued or entered by any Governmental Authority, in each case, that would be a Material Adverse Change. Each of the Seller and any Affiliate of the Seller is in compliance with the requirements of all Applicable Laws, a breach of any of which would be a Material Adverse Change.

Section 3.12 Earn-Out Product.

a. There is no injunction, claim, suit, action, citation, summons, subpoena, hearing, inquiry, investigation, complaint, arbitration, mediation, demand, decree or other dispute, disagreement, proceeding or claim by or with any Person against the Seller involving the Earn-Out Product that, if adversely determined, would reasonably be expected to result in a Material Adverse Change.

b. To the Knowledge of the Seller, there is no pending or threatened (in writing), and no event has occurred or circumstance exists that (with or without notice or lapse of time, or both) could reasonably be expected to give rise to or serve as a basis for any, action, suit or proceeding, or any investigation or claim by any Person to which the Seller or, to the Knowledge of the Seller, to which Counterparty, any Affiliate of Counterparty or any Sublicensee is or could be a party, and the Seller has not received any written notice of the foregoing, that claims that the manufacture, use, marketing, sale, offer for sale, importation or distribution of the Earn-Out Product by Counterparty, any Affiliate of Counterparty or any Sublicensees does or could infringe on any patent or other intellectual property rights of any other Person or constitute misappropriation of any other Person's trade secrets or other intellectual property rights. To the Knowledge of the Seller, there are no pending patent applications owned by any third party that, if issued, would limit or prohibit, in any material respect, the manufacture, use or sale of the Earn-Out Product by Counterparty, any Affiliate of Counterparty or any Sublicensees. To the Knowledge of the Seller, Counterparty is the sole and exclusive owner, or exclusive licensee, of all intellectual property rights underlying the Earn-Out Product. Except as set forth on Schedule 3.12(b), the Seller has not received any notice of any,

and to the Knowledge of the Seller, there is no, infringement of any of the intellectual property rights underlying the Earn-Out Product.

Section 3.13 Regulatory Matters.

a. All applications, submissions, information and data related to the Earn-Out Product submitted or utilized as the basis for any request to any Regulatory Agency by or on behalf of the Seller prior to the Sale Date were true and correct in all material respects as of the date of such submission or request, and, to the Knowledge of the Seller, any material updates, changes, corrections or modifications to such applications, submissions, information or data required to have been made under applicable laws or regulations have been submitted to the necessary Regulatory Agencies.

b. Neither the Seller, nor, to the Knowledge of the Seller, the Counterparty or any of its or their officers, employees, contractors or agents, is the subject of any pending or, to the Knowledge of the Seller, threatened investigation by the FDA or any other Regulatory Agency with regard to the Earn-Out Product that would reasonably be expected to result in a Material Adverse Change.

c. None of the Seller, any of its Subsidiaries and, to the Knowledge of the Seller, any third party manufacturer named in any NDA for the Earn-Out Product, has received from the FDA a "Warning Letter", Form FDA-483, "Untitled Letter", or similar material written correspondence or notice alleging violations of applicable laws and regulations enforced by the FDA, or any comparable material written correspondence from any other Regulatory Agency with regard to the Earn-Out Product or the manufacture, processing, packaging or holding thereof, the subject of which communication is unresolved and if determined adversely would, individually or in the aggregate, reasonably be expected to result in a Material Adverse Change.

d. Neither the Seller nor any of its officers, employees, contractors or agents made an untrue statement of material fact on, or material omissions from, any notifications, applications, approvals, reports and other submissions to the FDA or any similar Regulatory Agency with respect to the Earn-Out Product.

e. Prior to entering into the Counterparty Agreement, the Seller was in compliance with all applicable laws administered or issued by the FDA or any similar Regulatory Agency, including the FD&C Act, applicable requirements in FDA regulations, and any orders issued by the FDA or similar Regulatory Agencies, and all other laws regarding ownership, developing, testing, manufacturing, packaging, storage, import, export, disposal, marketing, distributing, promoting, and complaint handling or adverse event reporting for the Earn-Out Product, except to the extent that such failure to comply with such applicable laws would not be a Material Adverse Change.

Section 3.14 Counterparty Agreement.

a. Other than the Transaction Documents and the Counterparty Agreement, there is no contract, agreement or other arrangement (whether written or oral) to which the Seller or any of its Subsidiaries is a party or by which any of their respective assets or properties is bound or committed (i) that creates a Lien on, affects or otherwise relates to the Purchased Assets, the Earn-Out Product or the Counterparty Agreement, or (ii) for which breach, nonperformance, cancellation or failure to renew would be a Material Adverse Change.

b. Attached as Exhibit D hereto is a true, correct and complete copy of the Counterparty Agreement in effect on the Effective Date. The Seller has provided to the

Purchaser true, correct and complete copies of (i) any confidentiality agreement between Seller and Counterparty relating thereto that is currently in effect, (ii) all Quarterly Net Sales Statements, Annual Net Sales Statements, and Audit Reports provided under the Counterparty Agreement prior to the Effective Date, and (iii) all material notices and material correspondences delivered to, or by, the Seller pursuant to the Counterparty Agreement relating to the Purchased Assets or the Earn-Out Product since the Sale Date.

c. The Counterparty Agreement is in full force and effect and is the legal, valid and binding obligation of the Seller and Counterparty, enforceable against the Seller and Counterparty in accordance with its terms, subject, as to enforcement of remedies, to bankruptcy, insolvency, reorganization, moratorium or similar Applicable Laws affecting creditors' rights generally and general equitable principles. The execution and delivery of, and performance of obligations under, the Counterparty Agreement were and are within the powers of the Seller and, to the Knowledge of the Seller, Counterparty. The Counterparty Agreement was duly authorized by all necessary action on the part of, and validly executed and delivered by, the Seller and to the Knowledge of the Seller, Counterparty. The Seller is not in breach or violation of or in default under the Counterparty Agreement. There is to Seller's Knowledge no event or circumstance that, upon notice or the passage of time, or both, would constitute or give rise to any breach or default in the performance of the Counterparty Agreement by the Seller or Counterparty.

d. The Seller has not waived any rights or defaults under the Counterparty Agreement or released Counterparty, in whole or in part, from any of its obligations under the Counterparty Agreement. There are no oral waivers or modifications (or pending requests therefor) in respect of the Counterparty Agreement. Neither the Seller nor Counterparty has agreed to amend or waive any provision of the Counterparty Agreement, other than the Counterparty Consent.

e. To the Knowledge of the Seller, no event has occurred that would give the Seller or the Counterparty the right to terminate the Counterparty Agreement or allow Counterparty to cease paying Royalties thereunder or reduce any such payments other than in connection with Permitted Deductions. The Seller has not received any notice of an intention by Counterparty to terminate or breach the Counterparty Agreement, in whole or in part, or challenging the validity or enforceability of the Counterparty Agreement or the obligation to pay the Royalties under the Counterparty Agreement, or alleging that the Seller or Counterparty is in default of its obligations under the Counterparty Agreement. To the Knowledge of the Seller, there has been no default, violation or breach by Counterparty under the Counterparty Agreement that would reasonably be expected to result in a Material Adverse Change. The Seller has no intention of terminating the Counterparty Agreement and has not given Counterparty any notice of termination of the Counterparty Agreement, in whole or in part.

f. The amount of the Royalties paid under the Counterparty Agreement has not been and, to the Knowledge of the Seller, the amount of the Royalties due and payable under the Counterparty Agreement is not, as of the date hereof, subject to any claim against the Seller pursuant to any Royalty Reduction. To the Knowledge of the Seller, no event or condition currently exists that, upon notice, passage of time or otherwise, would permit Counterparty to make, or have the right to make, any Royalty Reduction against the Royalties. The Seller is not a party to any agreement (other than the Counterparty Agreement) providing for a sharing of, or providing for or permitting any Royalty Reduction against the Royalties payable under the Counterparty Agreement to the Seller. Counterparty has no express right of set-off under any contract or other agreement against the Royalties or any other amounts payable to the Seller under the Counterparty Agreement, other than rights of set-off expressly set forth in the Counterparty Agreement.

g. Seller has not consented to an assignment by Counterparty of any of Counterparty's rights or obligations under the Counterparty Agreement, and the Seller does not have Knowledge of any such assignment by Counterparty. Other than the Liens created in favor of the Purchaser set forth in Section 2.1(e) of this Purchase and Sale Agreement, the Seller has not assigned, in whole or in part, and has not granted, incurred or suffered to exist any Lien on the Counterparty Agreement or the Purchased Assets.

h. None of the Seller, Counterparty or any other Person has made any claim of indemnification under the Counterparty Agreement.

i. The Seller has not exercised its rights to conduct an audit under Section 2.13(e) of the Counterparty Agreement.

j. To the Knowledge of the Seller, the Seller has received all amounts in respect of Royalties owed to it under the Counterparty Agreement.

k. To the Knowledge of the Seller, Counterparty has not granted any sublicenses relating to the Earn-Out Product.

l. To the Knowledge of the Seller, none of Counterparty nor any of its Affiliates has entered into any Earn-Out Product Transaction.

m. To the Knowledge of the Seller, there has been no actual or alleged Specified Indemnity Claim and there exist no facts or circumstances that would reasonably be expected to result in a Specified Indemnity Claim.

n. Counterparty has no grounds to reduce, take an offset against, or otherwise withhold payment of the Royalties, whether pursuant to Section 2.13(a)(ii) of the Counterparty Agreement, Section 2.13(j) of the Counterparty Agreement or otherwise, other than deductions set forth in clause (i) of the definition of "Permitted Deductions".

o. To the Knowledge of the Seller, there are no Third Party License Payments that are required to be made to any Third Party with respect to the Earn-Out Product.

p. The Seller has not received any written notice advising the Seller that the obligation of Counterparty to pay Royalties will end before the expiration of the last to expire Applicable Patent Rights relating to the Earn-Out Product.

Section 3.15 Intellectual Property.

a. Schedule 3.15(a) of the Disclosure Schedule lists all Applicable Patent Rights. To the Knowledge of the Seller, Servier is the exclusive owner of the Applicable Patent Rights.

b. To the Knowledge of the Seller, except as set forth on Schedule 3.15(b) [/], there are no pending or threatened litigations, interferences, reexamination, oppositions, inter-partes review, post-grant review, derivation proceedings, or like procedures involving any Applicable Patent Rights.

c. To the Knowledge of the Seller, all of the Applicable Patent Rights are in full force and effect and had not lapsed, expired or otherwise terminated. To the Knowledge of the Seller, each issued claim within the Applicable Patent Rights is valid and enforceable. The Seller has not received any written notice relating to the lapse, expiration or other termination of

any of the issued Applicable Patent Rights, or any written legal opinion that alleges that any issued claim of the Applicable Patent Rights is invalid or unenforceable.

d. There is no Person who is, or claims to be, an inventor under any of the Applicable Patent Rights who is not a named inventor thereof. [**].

e. Seller has not, and, to the Knowledge of the Seller, Counterparty has not, received any written notice of any claim by any Person challenging inventorship or ownership of, the rights of the Seller (prior to the Sale Date) or rights of Counterparty (on or after the Sale Date), as applicable, in and to, or the patentability, validity or enforceability of, any issued claim of the Applicable Patent Rights, or asserting that the development, manufacture, importation, sale, offer for sale or use of the Earn-Out Product infringes or would reasonably be expected to infringe any patent or other intellectual property rights of such Person.

f. To the Knowledge of the Seller, the discovery, development and commercialization of the Earn-Out Product did not and has not infringed, violated or misused any patent or other intellectual property rights owned by any third party.

g. To the Knowledge of the Seller, the manufacture, use, marketing, sale, offer for sale, importation or distribution of the Earn-Out Product does not infringe, misappropriate or otherwise violate any patent rights or other intellectual property rights owned by any other Person.

h. To the Knowledge of the Seller, there has been no infringement of the Applicable Patent Rights by any third party.

i. To the Knowledge of the Seller as of the Sale Date, all required maintenance fees, annuities and like payments with respect to the Applicable Patent Rights had been timely paid.

Section 3.16 UCC Matters. The Seller's exact legal name is, and for the preceding 10 years has been, "Agios Pharmaceuticals, Inc." The Seller's principal place of business is, and for the preceding 10 years has been, located in Cambridge, Massachusetts. The Seller's jurisdiction of organization is, and for the preceding 10 years has been, the State of Delaware. The Seller's organizational identification number (within the meaning of Section 9-516(b)(5)(C)(iii) of the UCC) is 4403099.

Section 3.17 Margin Stock. The Seller is not engaged in the business of extending credit for the purpose of buying or carrying margin stock, and no portion of the Purchase Price shall be used by the Seller for a purpose that violates Regulation T, U or X promulgated by the Board of Governors of the Federal Reserve System from time to time.

Section 3.18 Investment Company Act. The Seller is not an "investment company" as such term is defined in the Investment Company Act of 1940, as amended.

ARTICLE 4
REPRESENTATIONS AND WARRANTIES OF THE PURCHASER

Each Purchaser hereby represents and warrants, severally and not jointly, to the Seller as of the date hereof as follows:

Section 4.1 Organization. Such Purchaser is duly formed or organized and, to the extent such concepts exist in its jurisdiction of organization, validly existing and in good

standing under the laws of its jurisdiction of organization and has all powers and authority, and all licenses, permits, franchises, authorizations, consents and approvals of all Governmental Authorities, required to own its property and conduct its business as now conducted.

Section 4.2 No Conflicts. None of the execution and delivery by such Purchaser of any of the Transaction Documents to which such Purchaser is party, the performance by such Purchaser of the obligations contemplated hereby or thereby or the consummation of the transactions contemplated hereby or thereby will contravene, conflict with, result in a breach, violation, cancellation or termination of, constitute a default (with or without notice or lapse of time, or both) under, require prepayment under, give any Person the right to exercise any remedy or obtain any additional rights under, or accelerate the maturity or performance of or payment under, in any respect, (i) any Applicable Law or any judgment, order, writ, decree, permit or license of any Governmental Authority to which such Purchaser or any of its assets or properties may be subject or bound, (ii) any term or provision of any contract, agreement, indenture, lease, license, deed, commitment, obligation or instrument to which such Purchaser is a party or by which such Purchaser or any of its assets or properties is bound or committed or (iii) any term or provision of any of the organizational documents of such Purchaser.

Section 4.3 Authorization. Such Purchaser has all necessary powers and authority to execute and deliver, and perform its obligations under, the Transaction Documents to which it is party and to consummate the transactions contemplated hereby and thereby. The execution and delivery of each of the Transaction Documents to which such Purchaser is a party and the performance by such Purchaser of its obligations hereunder and thereunder have been duly authorized by such Purchaser. Each of the Transaction Documents to which such Purchaser is party has been duly executed and delivered by such Purchaser. Each of the Transaction Documents to which such Purchaser is party constitutes the legal, valid and binding obligation of such Purchaser, enforceable against such Purchaser in accordance with its respective terms, subject to applicable bankruptcy, insolvency, reorganization, moratorium or similar Applicable Laws affecting creditors' rights generally and general equitable principles.

Section 4.4 Governmental and Third Party Authorizations. The execution and delivery by such Purchaser of the Transaction Documents to which such Purchaser is party, the performance by such Purchaser of its obligations hereunder and thereunder and the consummation of any of the transactions contemplated hereunder and thereunder by such Purchaser do not require any consent, approval, license, order, authorization or declaration from, notice to, action or registration by or filing with any Governmental Authority or any other Person, except as described in Section 3.5.

Section 4.5 No Litigation. There is no (a) action, suit, arbitration proceeding, claim, demand, citation, summons, subpoena, investigation or other proceeding (whether civil, criminal, administrative, regulatory, investigative or informal) pending or, to the knowledge of such Purchaser, threatened by or against such Purchaser, at law or in equity, or (b) inquiry or investigation (whether civil, criminal, administrative, regulatory, investigative or informal) by or before a Governmental Authority pending or, to the knowledge of such Purchaser, threatened against such Purchaser, that, in each case, challenges or seeks to prevent or delay the consummation of any of the transactions contemplated by any of the Transaction Documents to which such Purchaser is party.

Section 4.6 No Competitor. Such Purchaser is not a Competitor.

ARTICLE 5
COVENANTS

The parties hereto covenant and agree as follows:

Section 5.1 Books and Records; Notices.

a. From and after the Effective Date, promptly (but in no event more than [**]) after receipt by the Seller of written notice of, or related to, any action, suit, claim, demand, dispute, investigation, arbitration or other proceeding (commenced or threatened in writing) relating to (i) any Transaction Document or the Counterparty Agreement or the transactions contemplated hereunder or thereunder, (ii) the Purchased Assets or (iii) any default or termination by Counterparty under the Counterparty Agreement, the Seller shall (x) inform the Purchaser's Representative in writing of the receipt of such notice and the substance thereof and (y) if such notice is in writing, furnish the Purchasers with a copy of such notice and any related materials with respect thereto.

b. The Seller shall keep and maintain, or cause to be kept and maintained, at all times full and accurate books and records adequate to reflect accurately all financial information it has received from Counterparty related to the Purchased Assets, and all amounts paid or received under the Counterparty Agreement related to the Purchased Assets. Notwithstanding the foregoing or anything in the Transaction Documents to the contrary, Seller shall have no obligation to keep or maintain information it or Counterparty delivers to Purchaser, except as required under Applicable Law.

c. From and after the Effective Date, promptly (but in no event more than [**]) following receipt by the Seller from Counterparty, any of its Affiliates or any Sublicensees of any written notice, certificate, offer, proposal, material correspondence, report or other material communication relating to or affecting the Purchased Assets, the Seller shall (i) inform the Purchaser's Representative in writing of such receipt and (ii) furnish the Purchasers with a copy of such notice, certificate, offer, proposal, correspondence, report or other communication. [**]. The Seller shall promptly furnish to the Purchasers a copy of any material communication relating to or affecting the Purchased Assets sent by the Seller to Counterparty, any of its Affiliates or any Sublicensees.

d. From and after the Effective Date, the Seller shall provide the Purchaser's Representative with written notice as promptly as practicable (and in any event within [**]) after obtaining Knowledge of any of the following: (i) the occurrence of a Bankruptcy Event in respect of the Seller; (ii) any breach or default by the Seller or Counterparty of or under any covenant, agreement or other provision of any Transaction Document to which it is party; (iii) any representation or warranty made by the Seller in any of the Transaction Documents or in any certificate delivered to the Purchasers pursuant to this Purchase and Sale Agreement shall prove to be untrue, inaccurate or incomplete in any material respect on the date as of which made; (iv) any change, effect, event, occurrence, state of facts, development or condition that would reasonably likely to result in a Material Adverse Change, (v) any allegation or claim by a third party that the making, having made, using, importing, offering for sale or selling of any Earn-Out Product infringes any intellectual property rights of such third party; or (vi) any third party making, having made, using, importing, offering for sale or selling of any product in a manner that infringes any intellectual property rights underlying the Earn-Out Product.

e. The Seller shall notify the Purchasers in writing not less than [**] prior to any change in, or amendment or alteration of, the Seller's (i) legal name, (ii) form or type of

organizational structure, (iii) jurisdiction of organization or (iv) organizational identification number (within the meaning of Section 9-516(b)(5)(C)(iii) of the UCC).

f. From and after the Effective Date, subject to applicable confidential restrictions (including Section 5.10) and Applicable Laws relating to securities matters, the Seller shall make available such other information within Seller's Knowledge as the Purchasers may, from time to time, reasonably request with respect to (i) the Purchased Assets, (ii) the Counterparty Agreement as to any matter related to the Purchased Assets, (iii) the Royalties, and (iv) the Earn-Out Products.

Section 5.2 Public Announcement. Except for a press release previously approved in form and substance by the Seller and the Purchasers or any other public announcement using substantially the same text as such press release, neither the Purchasers nor the Seller shall, and each party hereto shall cause its respective Affiliates not to, issue a press release or other public announcement or otherwise make any public disclosure with respect to the Transaction Documents, or the subject matter or any terms hereof or thereof (including the identity of any of the parties hereto), without the prior written consent of the other parties hereto (which consent shall not be unreasonably withheld or delayed), except as may be required by applicable law or stock exchange rule (in which case the party hereto required to make the press release or other public announcement or disclosure shall allow the other parties hereto reasonable time to comment on, and, if applicable, reasonably direct the disclosing party to seek confidential treatment in respect of portions of, such press release or other public announcement or disclosure in advance of such issuance).

Section 5.3 Efforts; Further Assurances.

a. Subject to the terms and conditions of this Purchase and Sale Agreement, from and after the Effective Date, the Seller and each of the Purchasers, severally and not jointly, shall use its reasonable best efforts to take, or cause to be taken, all actions and to do, or cause to be done, all things necessary under Applicable Laws to consummate the transactions contemplated by the Transaction Documents to which the Seller or the Purchaser(s), as applicable, is party, including to perfect the sale, contribution, assignment, transfer, conveyance and granting of the Purchased Assets to the Purchasers pursuant to this Purchase and Sale Agreement. Following the Effective Date, the Purchasers and the Seller agree to take, or cause to be taken, all actions and to do, or cause to be done, all things necessary under Applicable Laws to (i) execute and deliver such other documents, certificates, instruments, agreements and other writings and to take such other actions as may be necessary or desirable, or reasonably requested by the other party hereto, in order to consummate or implement expeditiously the transactions contemplated by any Transaction Document to which the Seller or the Purchaser(s), as applicable, is party, (ii) perfect, protect, more fully evidence, vest and maintain in the Purchasers good, valid and marketable rights and interests in and to the Purchased Assets free and clear of all Liens (other than those Liens created in favor of the Purchasers pursuant to Section 2.1(e) hereof), (iii) create, evidence and perfect each Purchaser's first priority back-up security interests granted pursuant to Sections 2.1(e), and (iv) enable the Purchasers to exercise or enforce any of the Purchasers' rights under any Transaction Document to which the Seller or such Purchaser as applicable, is party, including following the Effective Date.

b. From and after the Effective Date, the Seller and each of the Purchasers, severally and not jointly, shall cooperate and provide assistance as reasonably requested by any other party hereto, at the expense of such other party hereto (except as otherwise set forth herein), in connection with any litigation, arbitration, investigation or other proceeding (whether threatened, existing, initiated or contemplated prior to, on or after the date hereof) to which the other party hereto, any of its Affiliates or controlling persons or any of their respective officers,

directors, equityholders, controlling persons, managers, agents or employees is or may become a party or is or may become otherwise directly or indirectly affected or as to which any such Persons have a direct or indirect interest, in each case relating to any Transaction Document, the Purchased Assets or the transactions described herein or therein but in all cases excluding any litigation brought by the Seller (for itself or on behalf of any of its Affiliates and any and all of their respective partners, directors, managers, members, officers, employees, agents and controlling Persons) against any Purchaser or brought by any Purchaser (for itself or on behalf of its Affiliates and any and all of their respective partners, directors, managers, members, officers, employees, agents and controlling Persons) against the Seller.

c. Without limiting any other obligation of the Seller under this Purchase and Sale Agreement, from and after the Effective Date, the Seller shall comply with all Applicable Laws with respect to the Transaction Documents to which it is a party and the Counterparty Agreement, the violation of which would reasonably be expected to result in a Material Adverse Change.

d. From and after the Effective Date, the Seller shall not enter into any contract, agreement or other legally binding arrangement (whether written or oral), or grant any right to any other Person, in any case that would (i) reasonably be expected to result in a Material Adverse Change or (ii) reasonably be expected to conflict with the Transaction Documents or serve or operate to limit, circumscribe or alter any of the Purchasers' rights under the Transaction Documents (or the Purchasers' ability to exercise any such rights) or result in a default of Seller's obligations under the Transaction Documents or the Counterparty Agreement; provided, that the Seller's relationship with Counterparty in respect of the subject matter of this Section 5.3(d) shall be governed by Section 5.5.

Section 5.4 Payments on Account of the Purchased Assets and Payments Generally.

a. Notwithstanding the terms of the Counterparty Instruction, if Counterparty, any Sublicensee or any other Person makes any future payment in respect of the Purchased Assets to the Seller (or any of its Affiliates), then (i) the portion of such payment that represents Royalties shall be held by the Seller (or such Affiliate) in trust for the benefit of the Purchasers in a segregated account, (ii) the Seller (or such Affiliate) shall have no right, title or interest whatsoever in such portion of such payment and shall not create or suffer to exist any Lien thereon (other than Liens granted in favor of the Purchasers by Section 2.1(e)), and (iii) the Seller (or such Affiliate) promptly, and in any event no later than [**] following the receipt by the Seller (or such Affiliate) of such portion of such payment, shall remit such portion of such payment to the Deposit Account pursuant to Section 5.4(b) in the exact form received with all necessary endorsements.

b. The Seller shall make all payments required to be made by it to each Purchaser pursuant to this Purchase and Sale Agreement (including (i) any payment of Royalties, (ii) any payment by the Seller pursuant to Section 5.4(d); (iii) any payment by the Seller of amounts pursuant to Section 5.6, (iv) any payment of amounts to gross up Seller for any Specified Tax Withholding pursuant to Section 5.7, and (v) any payment paid to the Purchasers pursuant to Section 7.1) by wire transfer of immediately available funds, without set-off, off-set, deduction or withholding for or on account of any Taxes (subject to Section 5.7(b)) (provided that such Purchaser has delivered to the Seller a properly executed IRS Form W-8IMY (with applicable certifications or attachments), IRS Form W-8BEN-E, or other applicable IRS withholding form, establishing entitlement to an exemption from withholding under a United States income Tax treaty, or other appropriate form in order to avoid Tax withholding), to the Deposit Account as set forth on Schedule 1.2 (or to such other account as Purchaser's Representative shall notify the Seller in writing from time to time). The Seller and Purchasers

agree that if Purchaser delivers a properly executed IRS Form W-8IMY, the Person for which a Purchaser is acting as an intermediary shall be treated as having received payments pursuant to this Purchase and Sale Agreement directly from Seller for U.S. federal income tax purposes.

c. Each Purchaser shall make all payments required to be made by it to the Seller pursuant to this Purchase and Sale Agreement by wire transfer of immediately available funds, without set-off, off-set, deduction or withholding for or on account of any Taxes (except as otherwise provided in Section 5.7) (provided that the Seller has delivered to such Purchaser a properly executed IRS Form W-9 or other appropriate form in order to avoid Tax withholding), to the Seller Account.

d. If Counterparty, any Affiliate of Counterparty or any Sublicensee takes any Royalty Reduction against Royalties (other than for any prior over-payment of Royalties actually made to the Purchasers with respect to the time period on or after July 1, 2022 or as a result of a Credit Event), then the Seller shall cause the amount of such Royalty Reduction (or portion thereof, as the case may be) to be paid promptly (but in no event later than [**] following such Royalty Reduction) to the Deposit Account. For the avoidance of doubt, nothing herein or in any other Transaction Document shall provide recourse by the Purchaser to the Seller as a result of any failure by a Counterparty to generate Net Sales unless such failure results from the breach by the Seller of a representation, warranty, or covenant hereunder, and no such failure by a Counterparty to generate Net Sales shall be deemed a Royalty Reduction hereunder.

e. Unless and until this Purchase and Sale Agreement is terminated pursuant to Section 8.1, the Seller shall not amend, modify, supplement, restate, waive or change the Counterparty Instruction except as provided in Section 5.11.

Section 5.5 Counterparty Agreement.

a. From and after the Effective Date, the Seller shall perform and comply in all material respects with its duties and obligations under the Counterparty Agreement and shall otherwise act as reasonably instructed from time to time by the Purchasers under the Counterparty Agreement in respect of the Purchased Assets. From and after the Effective Date, the Seller (i) shall not forgive, release or compromise any amount owed to or becoming owing to it under the Counterparty Agreement related to the Purchased Assets, (ii) shall not assign, cancel or terminate (or consent to any cancellation or termination of) the Counterparty Agreement, or amend, modify, supplement, restate or waive any provision of the Counterparty Agreement related to the Purchase Assets, (iii) shall not enter into any new agreement or legally binding arrangement in respect of the Purchased Assets, (iv) shall not waive any obligation of, or grant any consent to, Counterparty under or in respect of the Purchased Assets and (v) shall not agree to do any of the foregoing, except, in each case, as reasonably instructed by the Purchasers. The Seller shall promptly (and in any case within [**] of receipt thereof) deliver to the Purchaser copies of all fully-executed or definitive writings related to the matters set forth in clauses (ii), (iii) or (iv) or (v).

b. From and after the Effective Date, the Seller shall not, except as reasonably instructed by the Purchaser's Representative (and at Purchasers sole cost and expense), grant or withhold any consent, exercise or waive any right or option, and shall not, in contravention of any instruction by the Purchaser's Representative, fail to exercise any right or option or exercise or fail to exercise any action in or under the Counterparty Agreement affecting or relating to the Purchased Assets; provided that neither Purchaser's Representative nor any Purchaser shall issue any instruction to Seller or exercise any action that would be reasonably likely to reduce the Royalties.

c. If (i) the Seller receives a written notice from Counterparty (A) terminating the Counterparty Agreement (in whole or in part) or any of its obligations thereunder, (B) alleging any breach of or default under the Counterparty Agreement by the Seller, (C) asserting the existence of any facts, circumstances or events that, alone or together with other facts, circumstances or events, would reasonably be expected (with or without the giving of notice or passage of time, or both) to give rise to a breach of or default under the Counterparty Agreement by the Seller or the right to terminate the Counterparty Agreement (in whole or in part) or any of its obligations thereunder by Counterparty, (D) that would otherwise reasonably be expected to result in a Material Adverse Change or (E) any other material correspondence relating to the foregoing, or (ii) the Seller otherwise obtains Knowledge of any fact, circumstance or event that, alone or together with other facts, circumstances or events, would reasonably be expected (with or without the giving of notice or passage of time, or both) to give rise to a breach of or default under the Counterparty Agreement by the Seller or give rise to the right of Counterparty to terminate the Counterparty Agreement (in whole or in party) or any of its obligation thereunder by Counterparty or would otherwise reasonably be expected to result in a Material Adverse Change, in each case, the Seller shall (A) promptly (and in any event within [**]) give a written notice to the Purchaser's Representative describing the material details thereof, including a copy of any written notice received from Counterparty, and, in the case of any such breach or default or alleged breach or default by the Seller, describing in reasonable detail any corrective action the Seller proposes to take, and (B) in the case of any breach or default or alleged breach or default by the Seller, use its best efforts to promptly cure such breach or default.

d. If Seller obtains Knowledge of a breach of or default under, or an alleged breach of or default under, the Counterparty Agreement by Counterparty or of the existence of any facts, circumstances or events that, alone or together with other facts, circumstances or events, would reasonably be expected (with or without the giving of notice or passage of time, or both) to give rise to a breach of or default under the Counterparty Agreement by Counterparty or the right to terminate the Counterparty Agreement (in whole or in part) by the Seller, in each case, the Seller shall (i) promptly (but in any event within [**]) give a written notice to the Purchaser's Representative and provide the Purchaser's Representative with a written summary of all material details thereof, and (ii) at the sole cost and expense of the Purchaser, act in accordance with the Purchaser's Representative's reasonable instructions to take such permissible actions (including commencing legal action against Counterparty and the selection of legal counsel reasonably satisfactory to the Purchaser's Representative) to enforce compliance by Counterparty with the relevant provisions of the Counterparty Agreement and to exercise any or all of the Purchaser's or the Seller's rights and remedies, whether under the Counterparty Agreement or by operation of law, with respect thereto. The proceeds of any enforcement action taken pursuant to the immediately preceding sentence to the extent compensating for losses arising from or relating to the Purchased Assets shall be considered to be Royalties for all purposes hereunder. Notwithstanding anything to the contrary contained in this Article V, nothing herein shall prevent, restrict or limit a Purchaser from directly enforcing, at the Purchaser's sole cost and expense, the Purchaser's entitlement to the Purchased Assets with counsel selected by such Purchaser in its sole discretion.

e. The Seller shall make available its relevant records and personnel to the Purchasers in connection with any prosecution of litigation by the Seller or the Purchasers against Counterparty to enforce any of the Purchasers' rights under the Counterparty Agreement, and provide reasonable assistance and authority to file and bring the litigation, including, if required to bring the litigation, being joined as a party plaintiff.

Section 5.6 Mergers, Consolidation and Asset Sales Involving Counterparty. If there occurs a merger or consolidation between the Seller, on the one hand, and Counterparty or any of

its Affiliates, on the other hand, a sale of all or substantially all of the Seller's assets to Counterparty or a sale or assignment of the Counterparty Agreement by the Seller to Counterparty, and in any such case the Purchasers' rights to the Purchased Assets or under this Purchase and Sale Agreement are diminished in any material respect, (i) the Seller (or its successor) shall pay to each Purchaser an amount in cash equal to any Royalties that it does not receive from the Counterparty on the same basis (in both amount and timing) as if such Purchaser's rights to the Purchased Assets or under this Purchase and Sale Agreement were not so diminished and (ii) such Purchaser's rights with respect to the Purchased Assets and the covenants of the Seller under this Purchase and Sale Agreement shall continue to apply on the same basis as if such Purchaser's rights to the Purchased Assets or under this Purchase and Sale Agreement were not diminished in such way.

Section 5.7 Tax Matters.

a. Notwithstanding anything to the contrary in the Transaction Documents, the Seller and the Purchasers, severally and not jointly, shall treat the transactions contemplated by this Purchase and Sale Agreement as a sale of the Purchased Assets for United States federal, state and local Tax purposes.

b. All payments to the Purchasers and the Seller under this Purchase and Sale Agreement shall be made without any deduction or withholding for or on account of any Tax, except as required by Applicable Law; provided, that, if any deduction or withholding of any Tax is required from any such payment under this Purchase and Sale Agreement or from any payment under the Counterparty Agreement by reason of the Seller being a party to the Counterparty Agreement or to the extent resulting from any action by the Seller, including any assignment or transfer by the Seller pursuant to Section 8.4 of this Agreement (a "Specified Tax Withholding"), then the Seller shall, within [**] of any Purchaser receiving any payment subject to such Specified Tax Withholding make a payment to such Purchaser so that, after making all such required deductions and withholdings (including any deductions and withholdings required with respect to any such additional payment), such Purchaser receives an amount equal to the amount that it would have received had no such deductions or withholdings been made. Notwithstanding the above, the parties agree that as long as the Purchasers provide the Seller with IRS withholding forms establishing entitlement to an exemption from withholding in accordance with Section 5.4(b), no such deduction or withholding is intended on any payment made to the Purchasers under this Purchase and Sale Agreement. If the Seller determines or becomes aware that any such deduction or withholding is required by Applicable Law with respect to any payment pursuant to the Counterparty Agreement or to be remitted by the Seller on any payment hereunder, (i) the Seller shall notify the Purchasers at least [**] in advance of such payment, (ii) the Seller shall use its commercially reasonable efforts to make such filings and take such other actions as may be specified by the Purchasers in order to permit an exemption from or reduction of withholding Tax imposed on or with respect to any payments made to the Purchasers under this Purchase and Sale Agreement or the Counterparty Agreement, and (iii) if such Tax is to be remitted by the Seller on any payment hereunder, the Seller shall timely pay to the applicable Governmental Authority the full amount deducted or withheld and provide Purchasers with proof of payment of such amounts to the applicable Governmental Authority within [**] of making such payment. For the avoidance of doubt, but subject to Article VII of this Purchase and Sale Agreement (to the extent there is any deduction or withholding of Taxes arising out of a breach by Seller of any representations, warranties or covenants that would be reimbursable under Article VII of this Purchase and Sale Agreement), Seller shall not be obligated to pay or otherwise reimburse Purchaser for any deduction or withholding for or on account of any Tax required in connection with payments made under this Purchase and Sale Agreement or from any payment under the Counterparty Agreement, other than in connection with a Specified Tax Withholding.

c. The parties hereto, severally and not jointly, agree not to take any position that is inconsistent with the provisions of this Section 5.7 on any Tax return or in any audit or other Tax-related administrative or judicial proceeding unless the other parties hereto have consented in writing to such actions. If there is an inquiry by any Governmental Authority of the Seller or any Purchaser related to the treatment described in this Section 5.7, the parties hereto shall cooperate with each other in responding to such inquiry in a reasonable manner which is consistent with this Section 5.7.

Section 5.8 Existence. From and after the Effective Date, the Seller shall (a) preserve and maintain its existence (provided, however, that, subject in all respects to Section 8.4, nothing in this Section 5.8(a) shall prohibit the Seller from entering into any merger, consolidation or amalgamation with, or selling or otherwise transferring all or substantially all of its assets to, and other Person if the Seller is the continuing or surviving entity or if the surviving or continuing or acquiring entity assumes (whether expressly or by operation of law) all of the obligations of the Seller), (b) preserve and maintain its rights, franchises and privileges unless failure to do any of the foregoing would not be a Material Adverse Change, (c) qualify and remain qualified in good standing in each jurisdiction where the failure to preserve and maintain such qualifications would be a Material Adverse Change, including appointing and employing such agents or attorneys in each jurisdiction where it shall be necessary to take action under this Purchase and Sale Agreement, and (d) comply with its organizational documents unless failure to do so would not be a Material Adverse Change.

Section 5.9 Audits; Underpayment of Royalties; Overpayment of Royalties.

a. From and after the Effective Date, the Seller shall not, without the prior written consent of Purchaser's Representative, and the Seller shall, upon the written request of Purchaser's Representative (and at the sole cost and expense of the Purchasers), cause an inspection or audit of Counterparty's books and records to be conducted pursuant to, and in accordance with, Section 2.13(e) of the Counterparty Agreement. For the purposes of exercising the Purchasers' rights pursuant to this Section 5.9, the Seller shall select such public accounting firm as Purchaser's Representative shall recommend for such purpose. The Seller shall provide to the Purchasers a copy of the summary of the preliminary conclusions of the public accounting firm, and Purchaser's Representative shall have the exclusive right to provide comments thereon pursuant to Section 2.13(e) of the Counterparty Agreement. The Seller shall also provide to the Purchasers copies of any audit reports summarizing the results of any audit of the records of Counterparty in respect of the payment of Royalties pursuant to Section 2.13(e) of the Counterparty Agreement. The Seller and the Purchasers agree that all of the expenses of any inspection or audit carried out for the benefit of the Purchasers that would otherwise be borne by the Seller pursuant to the Counterparty Agreement shall instead be borne by the Purchasers pro rata in proportion to their respective Specified Percentages, including such fees and expenses of such independent accountant as are to be borne by the Seller pursuant to Section 2.13(e) of the Counterparty Agreement together with the Seller's reasonable out-of-pocket costs and expenses incurred in connection with such examination or audit. The Seller will furnish to the Purchasers any inspection or audit report prepared in connection with such inspection or audit. The Purchasers shall have the right to require the Seller, in writing, at the sole cost and expense of the Purchasers (such expense to be shared by the Purchasers pro rata in proportion to their respective Specified Percentages), to exercise the Seller's rights under the Counterparty Agreement to cause Counterparty to cure any discrepancy identified in the relevant audit report in accordance with the Counterparty Agreement.

b. In the event of an underpayment of Royalties under the Counterparty Agreement in respect of aggregate annual Net Sales of the Earn-Out Product made in the U.S. Territory prior to July 1, 2022, the Seller shall retain the right to furnish to Counterparty an

invoice for the amount of such underpayment within [**] after the final determination thereof, and shall retain the right to instruct Counterparty to pay or cause to be paid to the Seller an amount in cash equal to such underpayment. In the event of an underpayment of Royalties under the Counterparty Agreement in respect of aggregate annual Net Sales of the Earn-Out Product made in the U.S. Territory on or after July 1, 2022, the Seller shall, upon the request of Purchaser's Representative, furnish to Counterparty an invoice created by Purchaser's Representative for the amount of such underpayment within [**] after the final determination thereof, and shall instruct Counterparty to pay or cause to be paid to the Deposit Account an amount in cash equal to such underpayment.

c. In the event of an overpayment of Royalties under the Counterparty Agreement received by the Seller in respect of aggregate annual Net Sales of the Earn-Out Product made in the U.S. Territory prior to July 1, 2022, the Seller shall (x) if the Counterparty chooses cash repayment of such overpayment pursuant to clause (A) in the second sentence of 2.13(a)(iv) or 2.13(e)(A) of the Counterparty Agreement, pay or cause to be paid to Counterparty the amount in cash equal to such overpayment within [**] following receipt of an invoice from Counterparty after the final determination thereof, or (y) if the Counterparty chooses to offset such overpayment pursuant to clause (B) in the second sentence of 2.13(a)(iv) or 2.13(e)(B) of the Counterparty Agreement, such offset shall be deemed to be a "Royalty Reduction" hereunder and Seller shall be obligated to reimburse Purchaser for such offset pursuant to (but not in duplication of) Section 5.4(d). In the event of an overpayment of Royalties under the Counterparty Agreement received by the Purchasers in respect of aggregate annual Net Sales of the Earn-Out Product made in the U.S. Territory on or after July 1, 2022, the Purchasers shall (x) if the Counterparty chooses cash repayment of such overpayment pursuant to clause (A) in the second sentence of 2.13(a)(iv) or 2.13(e)(A) of the Counterparty Agreement, pay or cause to be paid to Counterparty the amount in cash equal to such Purchaser's Applicable Percentage of such overpayment within [**] following receipt of an invoice from Counterparty after the after the final determination thereof, or (y) if the Counterparty chooses to offset such overpayment pursuant to clause (B) in the second sentence of 2.13(a)(iv) or 2.13(e)(B) of the Counterparty Agreement, such offset shall be deemed to be a "Permitted Deduction" hereunder for which the Seller shall not be obligated to reimburse Purchaser under this Purchase and Sale Agreement.

Section 5.10 Confidentiality. The Purchaser agrees to keep confidential the Counterparty Agreement, the Quarterly Net Sales Statements produced by Counterparty pursuant to Section 2.13(a)(iii) of the Counterparty Agreement, the Annual Net Sales Statements produced by Counterparty pursuant to Section 2.13(a)(iv) of the Counterparty Agreement, and any Audit Reports received pursuant to Section 2.13(e) of the Counterparty Agreement, in each case in accordance with or on terms no less restrictive than those set forth in Section 5.5 of the Counterparty Agreement.

Section 5.11 Deposit Account. The parties hereto agree to act reasonably in amending the Counterparty Instruction to reflect the Seller's irrevocable instruction to the Counterparty to pay the Royalties to any deposit account designated by Purchaser's Representative (which shall initially be the Deposit Account), and the Seller shall promptly deliver such amended Counterparty Instruction to the Counterparty.

ARTICLE 6
EFFECTIVE DATE

Section 6.1 Effective Date Deliverables. On the Effective Date:

a. the Seller shall deliver to the Purchasers the Bill of Sale executed by the Seller;

b. the Seller shall deliver to the Purchasers the Counterparty Instruction executed by the Seller;

c. the Seller shall deliver or cause to be delivered to the Purchasers an opinion of WilmerHale, special counsel to the Seller, dated the Effective Date and in form and substance satisfactory to the Purchasers and their counsel;

d. the Seller shall deliver to the Purchasers a certificate of an officer of the Seller, dated the Effective Date, (i) certifying as to the Seller's organizational documents and the attached resolutions adopted by the board of directors of the Seller authorizing the transactions contemplated by the Transaction Documents and (ii) setting forth the incumbency of the officer or officers of the Seller who have executed and delivered the Transaction Documents, including therein a signature specimen of each such officer;

e. [Reserved]

f. the Seller shall deliver to the Purchasers a valid, properly executed IRS Form W-9 certifying that the Seller is exempt from U.S. federal "backup" withholding tax;

g. the Seller shall deliver to Purchasers financing statements, in the forms attached as Exhibit G, naming Purchaser's Representative as Secured Party on behalf of the Purchasers, to create, evidence and perfect the sale, contribution, assignment, transfer, conveyance and grant of the Purchased Assets pursuant to Section 2.1(a) and the back-up security interest granted pursuant to Section 2.1(e);

h. each Purchaser shall have delivered to the Seller a valid, properly executed IRS Form W-8IMY (with applicable certifications or attachments), IRS Form W-8BEN-E, or other applicable IRS withholding form, certifying that such Purchaser is (or payments to such Purchaser are) exempt from U.S. federal withholding tax with respect to any and all payments pursuant to this Purchase and Sale Agreement;

i. each Purchaser shall deliver to the Seller a certificate of an officer of such Purchaser, dated the Effective Date, setting forth the incumbency of the officer or officers of such Purchaser who have executed and delivered the Transaction Documents, including therein a signature specimen of each such officer.

ARTICLE 7
INDEMNIFICATION

Section 7.1 Indemnification by the Seller. From and after the Effective Date, the Seller agrees to indemnify and hold each Purchaser and its Affiliates and any and all of their respective officers, directors, employees, consultants, representatives and advisers (each, a "Purchaser Indemnified Party") harmless from and against, and will pay to each Purchaser Indemnified Party the amount of, any and all Losses (including attorneys' fees) awarded against or incurred or suffered by such Purchaser Indemnified Party whether or not involving a third party claim, demand, action or proceeding, in each case of the foregoing arising out of (i) any breach of any representation, warranty or verification made by the Seller in any of the Transaction Documents to which the Seller is party or certificates given by the Seller to the Purchasers in writing pursuant to this Agreement, (ii) any breach of any covenant or agreement by the Seller under (A) any Transaction Document to which the Seller is party or (B) the Counterparty Agreement, (iii) any Excluded Liabilities and Obligations, and (iv) any fees, expenses, costs, liabilities or other amounts incurred or owed by the Seller to any brokers, financial advisors or comparable other Persons retained or employed by it in connection with the

transactions contemplated by this Purchase and Sale Agreement; provided, however, that Seller shall not be liable for the payment to any Purchaser Indemnified Party for any portion of such Losses resulting from such Purchaser Indemnified Party's gross negligence or willful misconduct as determined in a final, non-appealable judgment of a court of competent jurisdiction. Any amounts due to any Purchaser Indemnified Party hereunder shall be payable to the Seller to such Purchaser Indemnified Party within [**] of written demand.

Section 7.2 Indemnification by the Purchaser. Each Purchaser agrees, severally and not jointly, to indemnify and hold each of the Seller and its Affiliates and any and all of their respective officers, directors, employees, consultants, representatives and advisers (each, a "Seller Indemnified Party") harmless from and against, and will pay to each Seller Indemnified Party the amount of, any and all Losses (including attorneys' fees) awarded against or incurred or suffered by such Seller Indemnified Party whether or not involving a third party claim, demand, action or proceeding, arising out of (i) any breach of any representation, warranty or certification made by such Purchaser in any of the Transaction Documents to which such Purchaser is party or certificates given by such Purchaser in any of the Transaction Documents to which such Purchaser is party or certificates given by such Purchaser in writing pursuant hereto or thereto, (ii) any breach of or default under any covenant or agreement by such Purchaser pursuant to any Transaction Document to which such Purchaser is party and (iii) any fees, expenses, costs, liabilities or other amounts incurred or owed by such Purchaser to any brokers, financial advisors or comparable other Persons retained or employed by it in connection with the transaction contemplated by this Purchase and Sale Agreement; provided, however, that Purchasers shall not be liable for the payment to any Seller Indemnified Party for any portion of such Losses resulting from such Seller Indemnified Party's gross negligence or willful misconduct as determined in a final, non-appealable judgment of a court of competent jurisdiction. Any amounts due to any Seller Indemnified Party hereunder shall be payable by the Purchaser to such Seller Indemnified Party within [**] of written demand.

Section 7.3 Procedures. If any claim, demand, action or proceeding (including any investigation by any Governmental Authority) shall be brought or alleged against an indemnified party in respect of which indemnity is to be sought against an indemnifying party pursuant to Section 7.1 or Section 7.2, the indemnified party shall, promptly after receipt of notice of the commencement of any such claim, demand, action or proceeding, notify the indemnifying party in writing of the commencement of such claim, demand, action or proceeding, enclosing a copy of all papers served, if any; provided, that the omission to so notify such indemnifying party will not relieve the indemnifying party from any liability that it may have to any indemnified party under Section 7.1 or Section 7.2 unless, and only to the extent that, the indemnifying party is actually prejudiced by such omission. In the event that any such action is brought against an indemnified party and it notifies the indemnifying party of the commencement thereof in accordance with this Section 7.3, the indemnifying party will be entitled, at the indemnifying party's sole cost and expense, to participate therein and, to the extent that it may wish, to assume the defense thereof, with counsel reasonably satisfactory to such indemnified party (who shall not, except with the consent of the indemnified party, be counsel to the indemnifying party), and, after notice from the indemnifying party to such indemnified party of its election so to assume the defense thereof, the indemnifying party will not be liable to such indemnified party under this Article VII for any legal expenses subsequently incurred by such indemnified party in connection with the defense thereof other than reasonable costs of investigation. In any such proceeding, an indemnified party shall have the right to retain its own counsel, but the reasonable fees and expenses of such counsel shall be at the expense of such indemnified party unless (a) the indemnifying party and the indemnified party shall have mutually agreed to the retention of such counsel, (b) the indemnifying party has assumed the defense of such proceeding and has failed within a reasonable time to retain counsel reasonably satisfactory to such indemnified party or (c) the named parties to any such proceeding (including any impleaded parties) include both the

indemnifying party and the indemnified party and representation of both parties by the same counsel would be inappropriate due to actual or potential conflicts of interests between them based on the advice of counsel to the indemnified party, in which case the reasonable fees and expenses of such counsel shall be at the expense of the indemnifying party. It is agreed that the indemnifying party shall not, in connection with any proceeding or related proceedings in the same jurisdiction, be liable for the reasonable fees and expenses of more than one separate law firm (in addition to local counsel where necessary) for all such indemnified parties. The indemnifying party shall not be liable for any settlement of any proceeding effected without its written consent (such consent not to be unreasonably withheld), but, if settled with such consent or if there be a final judgment for the plaintiff, the indemnifying party agrees to indemnify the indemnified party from and against any Loss by reason of such settlement or judgment. No indemnifying party shall, without the prior written consent of the indemnified party (such consent not to be unreasonably withheld), effect any settlement, compromise or discharge of any claim or pending or threatened proceeding in respect of which any indemnified party is or could have been a party and indemnity could have been sought hereunder by such indemnified party, unless such settlement, compromise or discharge, as the case may be, (i) includes an unconditional written release of such indemnified party, in form and substance reasonably satisfactory to the indemnified party, from all liability on claims that are the subject matter of such claim or proceeding, (ii) does not include any statement as to an admission of fault, culpability or failure to act by or on behalf of any indemnified party and (iii) does not impose any obligation or restrictions on any indemnified party.

Section 7.4 Exclusive Remedy. Except in the case of fraud or intentional breach, following the Effective Date, the indemnification afforded by this Article VII shall be the sole and exclusive remedy for any and all Losses awarded against or incurred or suffered by a party hereto in connection with the transactions contemplated by the Transaction Documents, including with respect to any breach of any representation, warranty or certification made by a party hereto in any of the Transaction Documents or certificates given by a party hereto in writing pursuant hereto or thereto or any breach of or default under any covenant or agreement by a party hereto pursuant to any Transaction Document. Notwithstanding anything in this Purchase and Sale Agreement to the contrary, in the event of any breach or failure in performance of any covenant or agreement contained in any Transaction Document, the non-breaching party shall be entitled to specific performance, injunctive or other equitable relief pursuant to Section 8.2.

Section 7.1 Limitation of Liability. Notwithstanding anything in this Agreement to the contrary, (a) the Seller shall not have any liability under Section 7.1 in excess of [**], provided, that the foregoing limitation shall not apply to breach of any of the representations, covenants or agreements set forth in Sections 3.8 and 5.7, and (b) no Purchaser shall have any liability under Section 7.2 in excess of [**].

ARTICLE 8
MISCELLANEOUS

Section 8.1 Termination; Survival.

a. [Reserved].

b. This Purchase and Sale Agreement shall commence on the Effective Date, and this Purchase and Sale Agreement shall continue in full force and effect until there are no longer Royalties from the Earn-Out Product, at which point this Purchase and Sale Agreement shall terminate, except for any rights, obligations or claims of either party hereto that have accrued prior to such termination; provided, however, that the provisions of Article II, Section

5.2, Section 5.4(d), Section 5.7, Section 5.9, Article VII, Article VIII and Article IX shall survive such termination. Unless and until this Purchase and Sale Agreement shall have terminated in accordance with the prior sentence, all representations, warranties and covenants made herein and in any other Transaction Document or any certificate delivered pursuant to this Purchase and Sale Agreement shall survive the execution and delivery of this Purchase and Sale Agreement and the Effective Date. The rights hereunder to indemnification, payment of Losses or other remedies based on such representations, warranties and covenants shall not be affected by any investigation conducted with respect to, or any knowledge acquired (or capable of being acquired) at any time (whether before or after the execution and delivery of this Purchase and Sale Agreement or the Effective Date) in respect of the accuracy or inaccuracy of or compliance with, any such representation, warranty or covenant. The waiver of any condition based on the accuracy of any representation or warranty, or on the performance of or compliance with any covenant, shall not affect the rights hereunder to indemnification, payment of Losses or other remedies based on such representations, warranties and covenants. Promptly following the termination of this Purchase and Sale Agreement in accordance with the first sentence of this Section 8.1, the Purchasers shall deliver to Counterparty an irrevocable instruction (i) to pay to Seller or Seller's designee all payments of Royalties in respect of the Earn-Out Product under the Counterparty Agreement made after the date of such termination and (ii) to terminate delivery to Purchasers of all future copies of reports of the type Counterparty had been instructed to deliver to Purchasers under the Counterparty Instruction.

Section 8.2 Specific Performance. Each of the parties hereto acknowledges that the other party hereto will have no adequate remedy at law if it fails to perform any of its obligations under any of the Transaction Documents. In such event, each of the parties hereto agrees that the other party hereto shall have the right, in addition to any other rights it may have (whether at law or in equity), to specific performance of this Purchase and Sale Agreement.

Section 8.3 Notices. All notices and other communications under this Purchase and Sale Agreement shall be in writing and shall be by email with PDF attachment, facsimile, courier service or personal delivery to the following addresses, or to such other addresses as shall be designated from time to time by a party hereto in accordance with this Section 8.3:

If to the Seller, to it at:

Agios Pharmaceuticals, Inc.
88 Sidney St.
Cambridge, MA 02139
Attention: [**]
Email: [**]

with a copy to:

WilmerHale
60 State Street
Boston, MA 02109
Attention: George W. Shuster Jr.
Email: george.shuster@wilmerhale.com

If to the Purchasers, to the Purchaser's Representative at:

Sagard
161 Bay Street, Suite 5000
Toronto, ON M5J 2S1

Canada
Attention: [**]
E-mail: [**]

with a copy to:

Mintz, Levin, Cohn, Ferris, Glovsky & Popeo, PC
666 Third Avenue
New York, NY 10017
Attention: Richard Gervase
E-mail: rgervase@mintz.com

Section 8.4 Successors and Assigns. The provisions of this Purchase and Sale Agreement shall be binding upon and inure to the benefit of the parties hereto and their respective successors and permitted assigns. The Seller shall not be entitled to assign or otherwise transfer any Transaction Document or any of its obligations, rights or interests under any of the Transaction Documents, in whole or in part, by operation of law, merger, change of control or otherwise, without the prior written consent of the Majority Purchasers (such consent not to be unreasonably withheld, conditioned or delayed provided that such assignment is an assignment of all of Seller's rights and obligations under this Agreement and meets the provisions of Section 8.04(a)(ii), Section 8.4(a)(iii) and Section 8.4(b) below), and any purported assignment or transfer without such consent shall be void and of no effect; provided, however, that the Seller may, without the prior written consent of the Purchasers, assign all of its obligations and rights under this Purchase and Sale Agreement (in whole, and not in part) to any other Person with which it may merge or consolidate or to which it may sell all or substantially all of its assets (including the Counterparty Agreement), provided that (a) the assignee under such assignment (i) is a Qualified Assignee, (ii) has also been assigned the Counterparty Agreement in connection with such transaction, and (iii) agrees to be bound by the terms of the Transaction Documents and the Counterparty Agreement and furnishes a written agreement to the Purchaser Representative in form and substance reasonably satisfactory to the Purchaser's Representative to that effect, and (b) such transaction does not require either Counterparty to deduct or withhold from payments of the Royalties any additional taxes pursuant to the Counterparty Agreement or under Applicable Law that would not be reimbursable to Purchaser under this Purchase and Sale Agreement. Each Purchaser may assign any of its obligations and rights hereunder without restriction and without the consent of the Seller: (i) to any of its Affiliates, its limited partners and any feeder vehicles, managed funds and alternative investment vehicles each of them may establish, and (ii) to any other Person with the prior written consent of the Counterparties. The Purchaser shall give notice of any assignment to the Seller promptly after the occurrence thereof.

Section 8.5 Independent Nature of Relationship. The relationship between the Seller and the Purchaser is solely that of seller and purchaser, and neither the Seller nor the Purchaser has any fiduciary or other special relationship with the other party hereto or any of its Affiliates. This Purchase and Sale Agreement is not a partnership, joint venture agreement or similar agreement, and nothing contained herein or in any other Transaction Document shall be deemed to constitute the Seller and the Purchaser, and/or Counterparty, any Sublicensee or Affiliate thereof, as a partnership, an association, a joint venture or any other kind of entity or legal form for any purposes, including any Tax purposes. The parties hereto agree that they shall not take any inconsistent position with respect to such treatment in a filing with any Governmental Authority.

Section 8.6 Entire Agreement. This Purchase and Sale Agreement, together with the Exhibits hereto (which are incorporated herein by reference), and the other Transaction

Documents constitute the entire agreement between the parties hereto with respect to the subject matter hereof and supersede all prior agreements, understandings and negotiations, both written and oral, between the parties hereto with respect to the subject matter of this Purchase and Sale Agreement. No representation, inducement, promise, understanding, condition or warranty not set forth herein (or in the Exhibits hereto or the other Transaction Documents) has been made or relied upon by either party hereto. Neither this Purchase and Sale Agreement nor any provision hereof is intended to confer upon any Person other than the parties hereto any rights or remedies hereunder, except that Counterparty shall be a third-party beneficiary of the second to last sentence of Section 8.4.

Section 8.7 Governing Law.

a. THIS PURCHASE AND SALE AGREEMENT SHALL BE GOVERNED BY AND CONSTRUED IN ACCORDANCE WITH THE INTERNAL SUBSTANTIVE LAWS OF THE STATE OF NEW YORK WITHOUT REFERENCE TO THE RULES THEREOF RELATING TO CONFLICTS OF LAW OTHER THAN SECTION 5-1401 OF THE GENERAL OBLIGATIONS LAW OF THE STATE OF NEW YORK, AND THE OBLIGATIONS, RIGHTS AND REMEDIES OF THE PARTIES HEREUNDER SHALL BE DETERMINED IN ACCORDANCE WITH SUCH LAWS.

b. Each of the parties hereto hereby irrevocably and unconditionally submits, for itself and its property, to the non-exclusive jurisdiction of the Supreme Court of the State of New York sitting in New York County and of the United States District Court of the Southern District of New York, and any appellate court from any thereof, in any action or proceeding arising out of or relating to this Purchase and Sale Agreement or any other Transaction Document, or for recognition or enforcement of any judgment, and each of the parties hereto hereby irrevocably and unconditionally agrees that all claims in respect of any such action or proceeding may be heard and determined in such New York State court or, to the extent permitted by Applicable Law, in such federal court. Each of the parties hereto agrees that a final judgment in any such action or proceeding shall be conclusive and may be enforced in other jurisdictions by suit on the judgment or in any other manner provided by Applicable Law.

c. Each of the parties hereto hereby irrevocably and unconditionally waives, to the fullest extent it may legally and effectively do so, any objection that it may now or hereafter have to the laying of venue of any suit, action or proceeding arising out of or relating to this Purchase and Sale Agreement in any court referred to in Section 8.7(b). Each of the parties hereto hereby irrevocably waives, to the fullest extent permitted by Applicable Law, the defense of an inconvenient forum to the maintenance of such action or proceeding in any such court.

d. Each of the parties hereto irrevocably consents to service of process in the manner provided for notices in Section 8.3. Nothing in this Purchase and Sale Agreement will affect the right of any party hereto to serve process in any other manner permitted by Applicable Law. Each of the parties hereto waives personal service of any summons, complaint or other process, which may be made by any other means permitted by New York law.

Section 8.8 Waiver of Jury Trial. EACH PARTY HERETO HEREBY WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY RIGHT IT MAY HAVE TO A TRIAL BY JURY IN ANY LEGAL PROCEEDING DIRECTLY OR INDIRECTLY ARISING OUT OF OR RELATING TO THIS PURCHASE AND SALE AGREEMENT, OR THE TRANSACTIONS CONTEMPLATED HEREBY (WHETHER BASED ON CONTRACT, TORT OR ANY OTHER THEORY). EACH PARTY HERETO (A) CERTIFIES THAT NO REPRESENTATIVE, AGENT OR ATTORNEY OF THE OTHER PARTY HERETO HAS REPRESENTED. EXPRESSLY OR OTHERWISE, THAT THE

OTHER PARTY HERETO WOULD NOT, IN THE EVENT OF LITIGATION, SEEK TO ENFORCE THE FOREGOING WAIVER AND (B) ACKNOWLEDGES THAT IT AND THE OTHER PARTY HERETO HAVE BEEN INDUCED TO ENTER INTO THIS PURCHASE AND SALE AGREEMENT BY, AMONG OTHER THINGS, THE MUTUAL WAIVERS AND CERTIFICATIONS IN THIS SECTION 8.8.

Section 8.9 Severability. If one or more provisions of this Purchase and Sale Agreement are held to be invalid or unenforceable by a court of competent jurisdiction, such provision shall be excluded from this Purchase and Sale Agreement and the balance of this Purchase and Sale Agreement shall be interpreted as if such provision were so excluded and shall remain in full force and effect and be enforceable in accordance with its terms. Any provision of this Purchase and Sale Agreement held invalid or unenforceable only in part or degree by a court of competent jurisdiction shall remain in full force and effect to the extent not held invalid or unenforceable.

Section 8.10 Counterparts. This Purchase and Sale Agreement may be signed in any number of counterparts, each of which shall be an original, with the same effect as if the signatures thereto and hereto were upon the same instrument. This Purchase and Sale Agreement shall become effective when each party hereto shall have received a counterpart hereof signed by the other party hereto. Any counterpart may be executed by facsimile or other similar means of electronic transmission, including "PDF", and such facsimile or other electronic transmission shall be deemed an original.

Section 8.11 Amendments; No Waivers. Neither this Purchase and Sale Agreement nor any term or provision hereof may be amended, supplemented, restated, waived, changed or modified except with the written consent of the Seller, the Purchaser's Representative and the Majority Purchasers. No failure or delay by either party hereto in exercising any right, power or privilege hereunder shall operate as a waiver thereof nor shall any single or partial exercise thereof preclude any other or further exercise thereof or the exercise of any other right, power or privilege. No notice to or demand on either party hereto in any case shall entitle it to any notice or demand in similar or other circumstances. No waiver or approval hereunder shall, except as may otherwise be stated in such waiver or approval, be applicable to subsequent transactions. No waiver or approval hereunder shall require any similar or dissimilar waiver or approval thereafter to be granted hereunder. The rights and remedies herein provided shall be cumulative and not exclusive of any rights or remedies provided by Applicable Law.

Section 8.12 Table of Contents and Headings. The Table of Contents and headings of the Articles and Sections of this Purchase and Sale Agreement have been inserted for convenience of reference only, are not to be considered a part hereof and shall in no way modify or restrict any of the terms or provisions hereof.

ARTICLE 9
PURCHASER'S REPRESENTATIVE

Section 9.1 Appointment of Purchaser's Representative.

a. Sagard Healthcare Royalty Partners, LP, a Cayman Islands exempt limited partnership is hereby appointed Purchaser's Representative hereunder and under the other Transaction Documents and each Purchaser hereby authorizes Sagard Healthcare Royalty Partners, LP, in such capacity, to act as its agent in accordance with the terms hereof and the other Transaction Documents to perform, exercise and enforce any and all other rights and remedies of the Purchasers with respect to Seller, the Purchased Assets or otherwise related to any of same to the extent reasonably incidental to the exercise by Purchaser's Representative of

the rights and remedies specifically authorized to be exercised by Purchaser's Representative by the terms of this Agreement or any other Transaction Document.

b. Purchaser's Representative hereby agrees to act upon the express conditions contained herein and the other Transaction Documents, as applicable. In performing its functions and duties hereunder, Purchaser's Representative shall act solely as an independent agent of the Purchasers and does not assume and shall not be deemed to have assumed any obligation towards or relationship of agency or trust with or for Seller or any of its Subsidiaries.

Section 9.2 Seller's Delivery, Notice and Related Obligation to Purchasers; Instructions from Purchasers; Payments to Purchasers.

Anything to the contrary in any Transaction Document notwithstanding:

a. any obligation of the Seller or its Subsidiaries to inform, deliver or furnish information or documents to, or provide notice to Purchasers under the Transaction Documents shall be satisfied upon informing, delivering or providing notice to, as applicable, Purchaser's Representative;

b. to the extent any Purchaser has rights under the Transaction Documents to request information from Seller or make an instruction to Seller to enforce rights under the Counterparty Agreement or otherwise, such request or instruction shall be made by the Purchaser's Representative on behalf of the Purchasers; and

c. any payments to be made by the Counterparty or Seller to Purchasers under the Transaction Documents shall be made to the Purchaser's Representative for the benefit of the Purchasers.

Section 9.3 Powers and Duties. Each Purchaser irrevocably authorizes Purchaser's Representative to take such action on such Purchaser's behalf and to exercise such powers, rights and remedies hereunder and under the other Transaction Documents as are specifically delegated or granted to Purchaser's Representative by the terms hereof and thereof, together with such powers, rights and remedies as are reasonably incidental thereto. Purchaser's Representative shall have only those duties and responsibilities that are expressly specified herein and the other Transaction Documents. Purchaser's Representative may exercise such powers, rights and remedies and perform such duties by or through its agents or employees, and Purchaser's Representative shall not have, by reason hereof or any of the other Transaction Documents, a fiduciary relationship in respect of any Purchaser; and nothing herein or any of the other Transaction Documents, expressed or implied, is intended to or shall be so construed as to impose upon Purchaser's Representative any obligations in respect hereof or any of the other Transaction Documents except as expressly set forth herein or therein.

Section 9.4 General Immunity.

a. Purchaser's Representative shall not be responsible to any Purchaser for the execution, effectiveness, genuineness, validity, enforceability, collectability or sufficiency hereof or any other Transaction Document or for any representations, warranties, recitals or statements made herein or therein or made in any written or oral statements or in any financial or other statements, instruments, reports or certificates or any other documents furnished or made by Purchaser's Representative to the Purchasers or by or on behalf of Seller or any of its Subsidiaries to Purchaser's Representative or any Purchaser in connection with the Transaction Documents and the transactions contemplated thereby, nor shall Purchaser's Representative be required to ascertain or inquire as to the performance or observance of any of the terms,

conditions, provisions, covenants or agreements contained in any of the Transaction Documents or other breach of this Agreement or the other Transaction Documents or to make any disclosures with respect to the foregoing.

b. Neither Purchaser's Representative nor any of its officers, partners, directors, employees or agents shall be liable to Purchasers for any action taken or omitted by Purchaser's Representative under or in connection with any of the Transaction Documents except to the extent caused by Purchaser's Representative's gross negligence or willful misconduct, as determined by a court of competent jurisdiction in a final, non-appealable order. Purchaser's Representative shall be entitled to refrain from any act or the taking of any action (including the failure to take an action) in connection herewith or any of the other Transaction Documents or from the exercise of any power, discretion or authority vested in it hereunder or thereunder unless and until Purchaser's Representative shall have received instructions in respect thereof from the Majority Purchasers and, upon receipt of such instructions from the Majority Purchasers, Purchaser's Representative shall be entitled to act or (where so instructed) refrain from acting, or to exercise such power, discretion or authority, in accordance with such instructions. Without prejudice to the generality of the foregoing, (i) Purchaser's Representative shall be entitled to rely, and shall be fully protected in relying, upon any communication, instrument or document believed by it to be genuine and correct and to have been signed or sent by the proper Person or Persons, and shall be entitled to rely and shall be protected in relying on opinions and judgments of attorneys (who may be attorneys for Seller), accountants, experts and other professional advisors selected by it; and (ii) no Purchaser shall have any right of action whatsoever against Purchaser's Representative as a result of Purchaser's Representative acting or (where so instructed) refraining from acting hereunder or any of the other Transaction Documents in accordance with the instructions of Majority Purchasers.

c. Purchaser's Representative shall not be deemed to have knowledge or notice of any default or other breach of this Agreement or the other Transaction Documents unless it has actually received written notice thereof.

d. The agency hereby created shall in no way impair or affect any of the rights and powers of, or impose any duties or obligations upon, Purchaser's Representative in its individual capacity as a Purchaser hereunder. With respect to its participation in this Agreement and the other Transaction Documents as a Purchaser, Purchaser's Representative shall have the same rights and powers hereunder as any other Purchaser and may exercise the same as if it were not performing the duties and functions delegated to it hereunder, and the term "Purchaser" shall, unless the context clearly otherwise indicates, include Purchaser's Representative in its individual capacity.

Section 9.5 Purchasers' Representations, Warranties and Acknowledgment.

a. Each Purchaser represents and warrants to Purchaser's Representative that it has made its own independent investigation of the financial condition and affairs of Seller and Counterparty, and of the Purchased Assets, in connection with the entry into this Agreement, the other Transaction Documents and the transactions contemplated hereunder and thereunder and that it has made and shall continue to make its own appraisal of the condition (financial and otherwise) of Seller and Counterparty, and of the Purchased Assets. Purchaser's Representative shall not have any duty or responsibility, either initially or on a continuing basis, to make any such investigation or any such appraisal on behalf of Purchasers or to provide any Purchaser with any credit or other information with respect thereto, whether coming into its possession before paying the Purchase Price or at any time or times thereafter, and Purchaser's Representative shall not have any responsibility with respect to the accuracy of or the completeness of any information provided to Purchasers.

b. Each Purchaser, by delivering its signature page to this Agreement and funding its Purchase Price on the Effective Date, shall be deemed to have acknowledged receipt of, and consented to and approved, each Transaction Document and each other document required to be approved by Purchaser's Representative, Majority Purchasers or Purchasers, as applicable on the Effective Date.

c. EACH PURCHASER, IN PROPORTION TO ITS PRO RATA SHARE, SEVERALLY AGREES TO INDEMNIFY PURCHASER'S REPRESENTATIVE, ITS AFFILIATES AND ITS RESPECTIVE OFFICERS, PARTNERS, DIRECTORS, TRUSTEES, EMPLOYEES AND AGENTS OF PURCHASER'S REPRESENTATIVE (EACH, AN "INDEMNITEE AGENT PARTY") FOR AND AGAINST ANY AND ALL LIABILITIES, OBLIGATIONS, LOSSES, DAMAGES, PENALTIES, ACTIONS, JUDGMENTS, SUITS, COSTS, EXPENSES (INCLUDING COUNSEL FEES AND DISBURSEMENTS) OR DISBURSEMENTS OF ANY KIND OR NATURE WHATSOEVER WHICH MAY BE IMPOSED ON, INCURRED BY OR ASSERTED AGAINST SUCH INDEMNITEE AGENT PARTY IN EXERCISING ITS POWERS, RIGHTS AND REMEDIES OR PERFORMING ITS DUTIES HEREUNDER OR UNDER THE OTHER TRANSACTION DOCUMENTS OR OTHERWISE IN ITS CAPACITY AS SUCH INDEMNITEE AGENT PARTY IN ANY WAY RELATING TO OR ARISING OUT OF THIS AGREEMENT OR THE OTHER TRANSACTION DOCUMENTS, IN ALL CASES, WHETHER OR NOT CAUSED BY OR ARISING, IN WHOLE OR IN PART, OUT OF THE COMPARATIVE, CONTRIBUTORY, OR SOLE NEGLIGENCE OF SUCH INDEMNITEE AGENT PARTY; PROVIDED, NO PURCHASER SHALL BE LIABLE FOR ANY PORTION OF SUCH LIABILITIES, OBLIGATIONS, LOSSES, DAMAGES, PENALTIES, ACTIONS, JUDGMENTS, SUITS, COSTS, EXPENSES OR DISBURSEMENTS RESULTING FROM SUCH INDEMNITEE AGENT PARTY'S GROSS NEGLIGENCE OR WILLFUL MISCONDUCT, AS DETERMINED BY A COURT OF COMPETENT JURISDICTION IN A FINAL, NON-APPEALABLE ORDER. IF ANY INDEMNITY FURNISHED TO ANY INDEMNITEE AGENT PARTY FOR ANY PURPOSE SHALL, IN THE OPINION OF SUCH INDEMNITEE AGENT PARTY, BE INSUFFICIENT OR BECOME IMPAIRED, SUCH INDEMNITEE AGENT PARTY MAY CALL FOR ADDITIONAL INDEMNITY AND CEASE, OR NOT COMMENCE, TO DO THE ACTS INDEMNIFIED AGAINST UNTIL SUCH ADDITIONAL INDEMNITY IS FURNISHED; PROVIDED, IN NO EVENT SHALL THIS SENTENCE REQUIRE ANY PURCHASER TO INDEMNIFY ANY INDEMNITEE AGENT PARTY AGAINST ANY LIABILITY, OBLIGATION, LOSS, DAMAGE, PENALTY, ACTION, JUDGMENT, SUIT, COST, EXPENSE OR DISBURSEMENT IN EXCESS OF SUCH PURCHASER'S PRO RATA SHARE THEREOF; AND PROVIDED FURTHER, THIS SENTENCE SHALL NOT BE DEEMED TO REQUIRE ANY PURCHASER TO INDEMNIFY ANY INDEMNITEE AGENT PARTY AGAINST ANY LIABILITY, OBLIGATION, LOSS, DAMAGE, PENALTY, ACTION, JUDGMENT, SUIT, COST, EXPENSE OR DISBURSEMENT DESCRIBED IN THE PROVISO IN THE IMMEDIATELY PRECEDING SENTENCE.

Section 9.6 Successor Purchaser's Representative.

a. Purchaser's Representative may resign at any time by giving 30 days' (or such shorter period as shall be agreed by the Majority Purchasers) prior written notice thereof to the Purchasers and Seller. Upon any such notice of resignation, the Majority Purchasers shall have the right, upon 10 days' notice to Seller, to appoint a successor Purchaser's Representative. If no successor shall have been so appointed by the Majority Purchasers and shall have accepted such appointment within 30 days after the retiring Purchaser's Representative gives notice of its resignation, then the retiring Purchaser's Representative may, on behalf of the Purchasers appoint a successor Purchaser's Representative from among the Purchasers. Upon the

acceptance of any appointment as Purchaser's Representative hereunder by a successor Purchaser's Representative that successor Purchaser's Representative shall thereupon succeed to and become vested with all the rights, powers, privileges and duties of the retiring Purchaser's Representative, and the retiring Purchaser's Representative shall promptly execute and deliver to such successor Purchaser's Representative such amendments to financing statements, and take such other actions, as may be necessary or appropriate in connection with the assignment to such successor Purchaser's Representative of the security interests created under the Transaction Documents, whereupon such retiring Purchaser's Representative shall be discharged from its duties and obligations hereunder. After any retiring Purchaser's Representative's resignation hereunder as Purchaser's Representative, the provisions of this Article 9 shall inure to its benefit as to any actions taken or omitted to be taken by it while it was Purchaser's Representative hereunder.

b. Notwithstanding anything herein to the contrary, Purchaser's Representative may assign its rights and duties as Purchaser's Representative, as applicable, hereunder to its Affiliate without the prior written consent of, or prior written notice to, Seller or the Purchasers; provided that Seller and the Purchasers may deem and treat such assigning Purchaser's Representative as Purchaser's Representative for all purposes hereof, unless and until such assigning Purchaser's Representative provides written notice to Seller and the Purchasers of such assignment. Upon such assignment such Affiliate shall succeed to and become vested with all rights, powers, privileges and duties as Purchaser's Representative hereunder and under the other Transaction Documents.

c. Purchaser's Representative may perform any and all of its duties and exercise its rights and powers under this Agreement or under any other Transaction Document by or through any one or more sub-agents appointed by Purchaser's Representative. Purchaser's Representative and any such sub-agent may perform any and all of its duties and exercise its rights and powers by or through their respective Affiliates. All of the rights, benefits and privileges (including the exculpatory and indemnification provisions) of Article 9 shall apply to any such sub-agent and to the Affiliates of any such sub-agent, and shall apply to their respective activities as sub-agent as if such sub-agent and Affiliates were named herein.

Section 9.7 Security Grant.

a. Each Purchaser hereby further authorizes Purchaser's Representative, on behalf of and for the benefit of the Purchasers, to be the agent for and representative of the Purchasers with respect to the security interest granted in the Purchased Assets pursuant to Section 2.1(e) (the "Security Grant"). Without further written consent or authorization from Purchasers, Purchaser's Representative may (i) execute any documents or instruments necessary to release the Security Agreement upon termination of this Purchase and Sale Agreement, and (ii) enter into intercreditor, non-disturbance or similar agreement, in form and substance satisfactory to Purchaser's Representative in its sole discretion, with respect to any indebtedness of Seller.

b. Anything contained in any of the Transaction Documents to the contrary notwithstanding, Seller, Purchaser's Representative and each Purchaser hereby agree that no Purchaser shall have any right individually to realize upon the Security Grant, it being understood and agreed that all powers, rights and remedies under the Transaction Documents may be exercised solely by Purchaser's Representative, on behalf of Purchasers in accordance with the terms of the Transaction Documents.

Section 9.8 Agency for Perfection. Purchaser's Representative and each Purchaser hereby appoints each other Purchaser as agent and bailee for the purpose of perfecting the

Security Grant for Purchased Assets which, in accordance with Article 9 of the UCC, can be perfected only by possession or control (or where the security interest of a secured party with possession or control has priority over the security interest of another secured party) and Purchaser's Representative and each Purchaser hereby acknowledges that it holds possession of or otherwise controls any such Purchased Assets for the benefit of the Purchasers as secured party. Should any Purchaser obtain possession or control of any such Purchased Assets, such Purchaser shall notify Purchaser's Representative thereof, and, promptly upon Purchaser's Representative's request therefore shall deliver such Purchased Assets to Purchaser's Representative or in accordance with Purchaser's Representative's instructions.

Section 9.9 Reports and Other Information. (a) Any Purchaser may from time to time request of Purchaser's Representative in writing that Purchaser's Representative provide to such Purchaser a copy of any report or document provided by Seller to Purchaser's Representative that has not been contemporaneously provided by Seller to such Purchaser, and, upon receipt of such request, Purchaser's Representative promptly shall provide a copy of same to such Purchaser, and (b) to the extent that Purchaser's Representative is entitled, under any provision of the Transaction Documents, to request additional reports or information from Seller or its Subsidiaries, any Purchaser may, from time to time, reasonably request Purchaser's Representative to exercise such right as specified in such Purchaser's notice to Purchaser's Representative, whereupon Purchaser's Representative promptly shall request of Seller the additional reports or information reasonably specified by such Purchaser, and, upon receipt thereof from Seller, Purchaser's Representative promptly shall provide a copy of same to such Purchaser.

[SIGNATURE PAGE FOLLOWS]

IN WITNESS WHEREOF, the parties hereto have executed this Purchase and Sale Agreement as of the day and year first written above.

AGIOS PHARMACEUTICALS, INC.

By: /s/ Brian Goff
Name: Brian Goff
Title: Chief Executive Officer

SAGARD HEALTHCARE ROYALTY PARTNERS, LP

By: Sagard Healthcare Royalty Partners GP LLC, its general partner

By: /s/ Jason Sneah
Name: Jason Sneah
Title: Manager

By: /s/ Sacha Haque
Name: Sacha Haque
Title: General Counsel and Secretary

SAGARD HEALTHCARE PARTNERS CO-INVEST DESIGNATED ACTIVITY COMPANY

By: /s/ Kate Macken
Name: Kate Macken
Title: Director

Exhibit D

Counterparty Agreement

Incorporated by reference to Exhibit 2.1 of the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2021 filed with the Securities and Exchange Commission

Exhibit D

EMPLOYMENT AGREEMENT

This Employment Agreement (the "Agreement") is made as of December 5, 2022 by and between Agios Pharmaceuticals, Inc. (the "Company"), and Tsveta Milanova (the "Executive") (together, the "Parties").

RECITALS

WHEREAS the Company desires to employ the Executive as its Chief Commercial 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 January 3, 2023 (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 Commercial 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 Commercial 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:

(a) *Base Salary*. The Executive shall receive a base salary at the annualized rate of $510,000 (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.

(b) *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. 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.

(c) *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 $2,100,000, 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 $700,000 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 an annual PSU award in 2023 and annual equity grants beginning in 2024, in each case 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.

(d) *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.

(e) *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.

(f) *Severance.* The Company maintains an Amended and Restated Severance Benefits Plan, effective October 6, 2022 (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. 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.

(g) *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 D.

5. *Sign-on Payment*. The Executive will receive a one-time payment of $150,000. 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.

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 E 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/ Tsveta Milanova

Tsveta Milanova

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 January 3, 2023.

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 January 3, 2023.

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 January 3, 2023.

EXHIBIT D

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 E

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 E) 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]

CONSULTING AGREEMENT

THIS CONSULTING AGREEMENT (together with the attached **Business Terms Exhibit**, the "**Agreement**"), is entered into as of January 1, 2023 (the "**Effective Date**") by and between Agios Pharmaceuticals, Inc., a Delaware corporation with a principal place of business at 88 Sidney Street, Cambridge, MA 02139 ("**Agios**") and Richa Poddar, an individual with a main address at 32 Anderson Street, #1, Boston, MA 02114 (the "**Consultant**"). Agios desires to retain Consultant as an independent contractor with respect to certain services as described in this Agreement, and Consultant is willing to provide those services, all as provided in this Agreement.

1. Consulting Services. Agios hereby retains Consultant to provide consulting services to Agios as specified in the attached **Business Terms Exhibit** (the "**Consulting Services**") and as may be requested from time to time by Agios. Agios acknowledges that Consultant may engage its employees and consultants for the Consulting Services, provided that Consultant shall obligate its employees and consultants to comply with the terms and obligations of this Agreement and remains liable for performance of the Consulting Services or any breach of the terms and obligations by its employees and consultants hereunder.

2. Compensation. As full consideration for rendering the Consulting Services hereunder, Agios will compensate Consultant as described in the **Business Terms Exhibit**.

3. Performance. Consultant agrees to render the Consulting Services to Agios, or to its designee, (a) at such reasonably convenient times and places as Agios may direct, (b) under the general supervision of Agios, (c) in accordance with all applicable laws and regulations, and (d) on a best efforts basis. Consultant represents that they have not been debarred and are not under consideration to be debarred by the U.S. Food and Drug Administration from working in or providing consulting services to any pharmaceutical or biotechnology company under the Generic Drug Enforcement Act of 1992.

4. Compliance with Obligations to Third Parties. Consultant represents and warrants to Agios that the terms of this Agreement and Consultant's performance of Consulting Services does not and will not conflict with any of Consultant's obligations to any third parties. Consultant agrees not to use any trade secrets or other confidential information of any other person, firm, corporation, institution or other entity in connection with any of the Consulting Services. If Consultant is an employee of another company, Consultant represents and warrants that Consultant is permitted to enter into this Agreement. Consultant agrees not to make any use of any funds, space, personnel, facilities, equipment or other resources of a third party in performing the Consulting Services nor take any other action that would result in a third party owning or having a right in any Work Product (defined below), unless agreed upon in writing in advance by Agios.

5. Work Product. Consultant will promptly and fully disclose in confidence to Agios all inventions, discoveries, improvements, ideas, concepts, designs, processes, formulations, products, computer programs, works of authorship, databases, mask works, trade secrets, know-how, information, data, documentation, reports, research, creations and other products arising from or made in the performance of (solely or jointly with others) the Consulting Services (whether or not patentable or subject to copyright or trade secret protection) (the "**Work Product**"). Consultant assigns and agrees to assign to Agios all rights in the United States and throughout the world to Work Product. Consultant will keep and maintain adequate and current written records of all Work Product, and such records will be

available to and remain the sole property of Agios at all times. For purposes of the copyright laws of the United States, Work Product will constitute "works made for hire," except to the extent such Work Product cannot by law be "works made for hire." Consultant warrants that Consultant has and will have the right to transfer and assign to Agios ownership of all Work Product. Consultant will execute all documents, and take any and all actions needed, all without further consideration, in order to confirm Agios' rights as outlined above. In the event that Consultant should fail or refuse to execute such documents within a reasonable time, Consultant appoints Agios as attorney to execute and deliver any such documents on Consultant's behalf.

6. Confidentiality. Any scientific, technical, business or financial information furnished by or on behalf of Agios to Consultant and all Work Product ("**Confidential Information**") will be the property of Agios. During the Term and for a period of five (5) years thereafter, Consultant agrees not to (a) publish, disseminate or otherwise disclose Confidential Information to any third party or (b) use Confidential Information for any purpose other than in connection with rendering the Consulting Services. Consultant will exercise all reasonable precautions to physically protect the confidentiality of the Confidential Information. These obligations of non-disclosure and non-use will not apply to information which (i) was known to Consultant at the time it was disclosed, other than by previous disclosure by Agios, as evidenced by Consultant's written records at the time of disclosure, (ii) is at the time of disclosure or later becomes publicly known under circumstances involving no breach of this Agreement, or (iii) is lawfully and in good faith made available to Consultant by a third party who did not derive it, directly or indirectly, from Agios. Consultant may disclose Confidential Information to a governmental authority or by order of a court of competent jurisdiction, provided that the disclosure is subject to all applicable governmental or judicial protection available for like material and reasonable advance notice is given to Agios so that Agios may seek an appropriate protective order. Consultant will reasonably cooperate with Agios in its efforts to obtain such a protective order. Consultant understands and acknowledges the United States securities laws prohibit any person who has material non-public information about a company from purchasing or selling securities of such company, and prohibits communicating such information to any other person under circumstances where it is reasonably foreseeable that such person is likely to purchase or sell securities of such company. Consultant further acknowledges that Confidential Information can constitute such material non-public information.

7. Agios Property. All documents, data, records, materials, compounds, apparatus, equipment and other physical property furnished or made available to Consultant in connection with this Agreement will be and remain the sole property of Agios.

8. Publication; Publicity. Work Product may not be published or referred to, in whole or in part, by Consultant without the prior express written consent of Agios. Consultant will not use the name, logo, trade name, service mark, or trademark, or any simulation, abbreviation, or adaptation of same, or the name of Agios for publicity, promotion, or similar non-regulatory uses without Agios' prior written consent.

9. Expiration/Termination. This Agreement will commence on the Effective Date and continue for the **Term** specified in the **Business Terms Exhibit**, unless sooner terminated pursuant to the terms of this Section 9 or extended by mutual written agreement of the parties. Either party may terminate this Agreement at any time in the event of a material breach of a material provision of this Agreement upon written notice by the non-breaching party to the breaching party. Upon expiration or termination of this Agreement, neither Consultant nor Agios will have any further obligations under this Agreement, except that (a) Consultant will terminate all Consulting Services in progress in an orderly manner as soon as practicable and in accordance with a schedule agreed to by Agios, unless Agios specifies in the notice of termination that Consulting Services in progress should be completed, (b) Consultant will deliver to Agios any Agios property in its possession or control and all Work Product made through expiration or termination, (c) Agios will pay Consultant any monies due and owing Consultant, up to the time of termination or expiration, for Consulting Services actually performed and all authorized expenses actually incurred, (d) Consultant will promptly refund to Agios any monies paid by Agios in advance for Consulting Services not rendered, (e) Consultant will immediately return to Agios all Confidential Information and copies thereof provided to Consultant under this Agreement except for one (1) copy which Consultant may retain solely to monitor Consultant's surviving obligations of confidentiality, and

(f) the terms, conditions and obligations under Sections 4, 5, 6, 7, 8, 9 and 10 will survive expiration or termination.

10. Miscellaneous.

10.1 Independent Contractor Relationship. Nothing contained in this Agreement will be deemed to constitute Consultant an employee of Agios, it being the intent of the parties to establish an independent contractor relationship, nor will Consultant have authority to bind Agios in any manner whatsoever by reason of this Agreement. Consultant will at all times while on Agios premises observe all security and safety policies of Agios. Consultant will bear sole responsibility for paying and reporting its own applicable federal and state income taxes, social security taxes, unemployment insurance, workers' compensation, and health or disability insurance, retirement benefits, and other welfare or pension benefits. For the avoidance of doubt, during the Term, Consultant shall remain a "Participant" or "Eligible Participant" (as applicable) under the terms of Agios's 2013 Stock Incentive Plan and any stock option, restricted stock unit or performance share units agreements between Consultant and Agios (including, without limitation, the Restricted Stock Unit Agreement dated February 14, 2020, the Restricted Stock Unit Agreement dated February 10, 2021, and the Restricted Stock Unit Agreement dated March 1, 2022), and the vesting of any and all such awards shall continue in accordance with the vesting schedule and other terms applicable to such awards.

10.2 Taxes. Consultant will pay all required taxes on Consultant's income from Agios under this Agreement, if applicable. Consultant will provide Agios with Consultant's taxpayer identification number or social security number, as applicable.

10.3 Use of Name. Consultant consents to the use by Agios of Consultant's name on its website, in press releases, Company brochures, offering documents, presentations, reports or other documents in printed or electronic form, and any documents filed with the Securities and Exchange Commission provided that such materials or presentations accurately describe the nature of Consultant's relationship with or contribution to Agios.

10.4 Assignability and Binding Effect. The Consulting Services to be rendered by Consultant are personal in nature. Consultant may not assign or transfer this Agreement or any of Consultant's rights or obligations hereunder. In no event will Consultant assign or delegate responsibility for actual performance of the Consulting Services to any other natural person. This Agreement will be binding upon and inure to the benefit of the parties and their respective legal representatives, heirs, successors and permitted assigns.

10.5 Notices. All notices required or permitted under this Agreement must be in writing and must be given by addressing the notice to the address for the recipient set forth in this Agreement or at such other address as the recipient may specify in writing under this procedure. Notices to Agios will be marked "Attention: Legal Department". Notices will be deemed to have been given (a) three (3) business days after deposit in the mail with proper postage for first class registered or certified mail prepaid, or (b) one (1) business day after sending by nationally recognized overnight delivery service.

10.6 No Modification. This Agreement may be changed only by a writing signed by Consultant and an authorized representative of Agios.

10.7 Remedies. It is understood and agreed that Agios may be irreparably injured by a breach of this Agreement; that money damages would not be an adequate remedy for any such breach; and that Agios will be entitled to seek equitable relief, including injunctive relief and specific performance, without having to post a bond, as a remedy for any such breach, and such remedy will not be Agios' exclusive remedy for any breach of this Agreement.

10.8 Severability; Reformation. Any of the provisions of this Agreement which are determined to be invalid or unenforceable in any jurisdiction will be ineffective to the extent of such invalidity or unenforceability in such jurisdiction, without rendering invalid or unenforceable the remaining provisions hereof and without affecting the validity or enforceability of any of the other terms

of this Agreement in such jurisdiction, or the terms of this Agreement in any other jurisdiction. The parties will substitute for the invalid or unenforceable provision a valid and enforceable provision that conforms as nearly as possible with the original intent of the parties.

10.9 Waivers. No waiver of any term, provision or condition of this Agreement in any one or more instances will be deemed to be or construed as a further or continuing waiver of any other term, provision or condition of this Agreement. Any such waiver must be evidenced by an instrument in writing executed by Consultant or, in the case of Agios, by an officer authorized to execute waivers.

10.10 Entire Agreement. This Agreement constitutes the entire agreement of the parties with regard to its subject matter, and supersedes all previous written or oral representations, agreements and understandings between the parties on the subject matter; provided, that nothing in this Agreement modifies or supersedes the Confidential Separation Agreement and General Release agreement between Consultant ant Agios.

10.11 Governing Law. This Agreement will be governed by, construed, and interpreted in accordance with the laws of the Commonwealth of Massachusetts, without reference to principles of conflicts of laws.

10.12 Counterparts. This Agreement may be executed in any number of counterparts, each of which will be deemed an original, but all of which together will constitute one and the same instrument.

10.13 Headings. The section headings are included solely for convenience of reference and will not control or affect the meaning or interpretation of any of the provisions of this Agreement.

IN WITNESS WHEREOF, the parties hereto have executed this Agreement as of the Effective Date.

Agios Pharmaceuticals, Inc.	**Richa Poddar**
By: /s/ James Burns	By: /s/ Richa Poddar
Name: James Burns	
Title: Chief Legal Officer	

BUSINESS TERMS EXHIBIT

Consulting Agreement with Richa Poddar

1. **Consulting Services:**

Assistance with transition of US commercial launch-related matters and the Commercial function, and such other advisory services as may be requested by Agios from time to time in a manner that does not unreasonably interfere with Consultant's other professional obligations. The consulting services shall not exceed 8 hours per week without Consultant's approval; *provided*, that nothing in the Agreement (including this Exhibit) requires Agios to use Consultant's services for any specific or minimum number of hours during the Term; and *provided*, further, that Consultant's service level thereunder shall not affect her status as a consultant during the Term.

2. **Consideration/Compensation:**

During the Term, Agios will pay Consultant a monthly retainer fee of $18,750. For the avoidance of doubt, the schedule of the monthly retainer fees payable to Consultant is as follows:

- A monthly retainer fee of $18,750 for the period from the Effective Date through January 31, 2023;
- A monthly retainer fee of $18,750 for the period through February 28, 2023; and
- A monthly retainer fee of $18,750 for the period through March 31, 2023.

Agios will make each applicable monthly retainer payment within 15 days following the last day of the applicable month. The continued vesting, during the Term, of Consultant's equity awards granted to Consultant during her former employment with Agios shall also constitute consideration for this Agreement.

3. **Term:**

This Agreement will be for an initial term beginning on the Effective Date and ending on March 31, 2023, and may be extended in writing for additional period, at Agios' option and with Consultant's consent ("**Term**").

Exhibit 21.1

SUBSIDIARIES

Entity	State or other Jurisdiction of Incorporation or Organization
Agios Securities Corporation	Massachusetts
Agios Limited	Bermuda
Agios International Sarl (GmbH)	Switzerland
Agios Netherlands B.V.	The Netherlands
Agios Germany GmbH	Germany
Agios Italy S.R.L.	Italy
Agios France SARL	France

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (Nos. 333-262956, 333-266675, 333-267624, 333-269108, 333-253498, 333-236523, 333-229669, 333-223031, 333-216106, 333-209755, 333-201796, 333-193802, and 333-190101) and Form S-3 (No. 333-237930) of Agios Pharmaceuticals, Inc. of our report dated February 23, 2023 relating to the financial statements and the effectiveness of internal control over financial reporting, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
February 23, 2023

Exhibit 31.1

CERTIFICATION

I, Brian Goff, certify that:

1. I have reviewed this Annual Report on Form 10-K 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: February 23, 2023

/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 Annual Report on Form 10-K 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: February 23, 2023

/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 this Annual Report on Form 10-K of Agios Pharmaceuticals, Inc. (the "Company") for the fiscal year ended December 31, 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 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: February 23, 2023

/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 this Annual Report on Form 10-K of Agios Pharmaceuticals, Inc. (the "Company") for the fiscal year ended December 31, 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 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: February 23, 2023

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