UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 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, 2024

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 28, 2024 (based on the last reported sale price on the Nasdaq Global Select Market as of such date) was $2,416,161,200.

As of February 7, 2025, there were 57,296,167 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 2025 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, 2024 are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

Table of Contents

PART I

References to Agios

Throughout this Annual Report on Form 10-K, "the Company," "Agios," "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 fact, 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 "aim," "anticipate," "believe," "continue," "could," "estimate," "expect," "goal," "intend," "may," "might," "plan," "potential," "predict," "project," "should," "strategy," "target," "vision," "will," "would" or the negatives of these words 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 commercialization efforts and plans to commercialize PYRUKYND® (mitapivat);
- the initiation, timing, progress and results of current, planned and future preclinical studies and clinical trials, and our research and development programs;
- the potential of the isoforms of pyruvate kinase, including pyruvate kinase-R, or PKR, as therapeutic targets;
- the potential benefits of our products and product candidates targeting PKR, including PYRUKYND® (mitapivat) and tebapivat, and of our product candidate in our phenylalanine hydroxylase, or PAH, stabilizer program, AG-181, and our siRNA targeting the transmembrane serine protease 6, or TMPRSS6, gene, AG-236;
- 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, including our regulatory applications for approval of PYRUKYND® (mitapivat) for the treatment of adult patients with non-transfusion-dependent and transfusion-dependent alpha- or beta-thalassemia;
- our strategic vision;
- the timing, likelihood and amount of royalty payments we may receive from Servier Pharmaceuticals LLC with respect to certain U.S. net sales of vorasidenib;
- the amount and timing of future milestone and royalty payments potentially payable to Alnylam Pharmaceuticals, Inc. pursuant to the license agreement entered into in July 2023;
- the implementation of our business model and strategic plans for our business, product candidates and technology;
- our commercialization, sales, 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;
- our estimates regarding our expenses, future revenue, capital requirements and needs for additional financing; and
- the potential impact of public health epidemics or pandemics, global economic developments and geopolitical events on our business, operations, strategy and goals.

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. 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 as well as our own estimates of potential market opportunities. 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® 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-stage product candidates, including the potential approval of PYRUKYND® for the treatment of thalassemia or sickle cell disease, or SCD, in the United States 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.
- The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and positive results of completed clinical trials do not necessarily predict success in future clinical trials. The results of completed clinical trials of PYRUKYND® for the treatment of PK deficiency and thalassemia are not predictive of our ongoing clinical trials of PYRUKYND® in other indications, such as SCD, and the results of our early-stage clinical trials of tebapivat are not predictive of our later stage clinical trials of tebapivat.
- Interim and preliminary data from clinical trials that we announce or publish from time to time may change as more patient data becomes available and are subject to audit and verification procedures that could result in material changes in the final data.
- 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.
- 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 they are approved.
- We provide certain development estimates related to the development and regulatory approval of PYRUKYND® and our product candidates. If we do not achieve our projected development or regulatory approval estimates in the timeframes we announce and expect, the commercialization of our products may be delayed and, as a result, our stock price may decline.
- 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 indications for which we are developing PYRUKYND® 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 fund our operating expenses and capital expenditures, we will need to raise capital, and if we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.
- We have historically incurred operating losses. We expect to incur losses in the future and may never achieve or maintain profitability. Our net income for the year ended December 31, 2024 was $673.7 million, our net loss for the year ended December 31, 2023 was $352.1 million and our net loss for the year ended December 31, 2022 was $231.8 million. The net income we generated in the year ended December 31, 2024 was primarily due to the sale of the Vorasidenib Royalty Rights to Royalty Pharma and our receipt of the Vorasidenib Milestone Payment discussed below in Item 1. *Business*. As of December 31, 2024, we had an accumulated deficit of $148.9 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 may 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 medicines for rare diseases, with a focus on classical hematology. 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. 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. 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.

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. PYRUKYND® is approved for use by the U.S. Food and Drug Administration, or FDA, for the treatment of hemolytic anemia in adults with PK deficiency in the United States and by the European Commission for the treatment of PK deficiency in adult patients in the European Union, or EU. Additionally, 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 December 2024, we announced that we submitted a supplemental new drug application, or sNDA, to the FDA for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia, which was accepted with standard review by the FDA and granted a Prescription Drug User Fee Act, or PDUFA, goal date of September 7, 2025. Also in December 2024, we announced that we submitted a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia.

In addition, we are currently evaluating PYRUKYND® in Phase 3 clinical trials for the treatment of sickle cell disease, or SCD, and in pediatric patients with PK deficiency. We are also developing (i) tebapivat, a novel PK activator, for the potential treatment of lower-risk myelodysplastic syndromes, or LR MDS, and hemolytic anemias; (ii) AG-181, our phenylalanine hydroxylase, or PAH, stabilizer for the potential treatment of phenylketonuria, or PKU; and (iii) AG-236, an siRNA in-licensed

from Alnylam Pharmaceuticals, Inc., or Alnylam, targeting the transmembrane serine protease 6, or TMPRSS6 gene for the potential treatment of polycythemia vera, or PV.

Alnylam License Agreement

In accordance with the license agreement we entered into with Alnylam in July 2023, we made an up-front payment to Alnylam and recognized in-process research and development of $17.5 million in the year ended December 31, 2023. We will also pay Alnylam for certain expenses associated with the development of AG-236, an siRNA targeting the TMPRSS6 gene, and these will be recorded in our consolidated statements of operations as incurred. Additionally, we are responsible to pay up to $130.0 million in potential development and regulatory milestones, in addition to sales milestones as well as tiered royalties on annual net sales, if any, of licensed products, which may be subject to specified reductions and offsets. Because the acquired assets under the license agreement with Alnylam do not meet the definition of a business in accordance with Accounting Standards Codification, or ASC, 805, *Business Combinations*, we accounted for the agreement as an asset acquisition.

Sale of Oncology Business to Servier and Sale of Contingent Payments

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, or IDH, 1 or 2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), or the Vorasidenib Milestone Payment, 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, or the Vorasidenib Royalty Rights. The Vorasidenib Milestone Payment, Vorasidenib Royalty Rights and royalty payments related to TIBSOVO® are referred to as contingent payments and recognized as income when realizable. 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 agreed to conduct certain clinical development activities within the IDHIFA® development program.

In October 2022, we sold our rights to future contingent payments associated with the royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through the loss of exclusivity 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.

In August 2024, the FDA approved vorasidenib for adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, following surgery including biopsy, sub-total resection, or gross total resection. In September 2024, we received the Vorasidenib Milestone Payment from Servier and recognized income of $200.0 million within the milestone payment from gain on sale of oncology business line item in our consolidated statements of operations for the year ended December 31, 2024. In May 2024, we entered into a purchase and sale agreement to sell the Vorasidenib Royalty Rights to Royalty Pharma Investments 2019 ICAV, or Royalty Pharma, for $905.0 million in cash, or the Upfront Payment. The sale was contingent upon FDA approval of vorasidenib and other customary closing conditions.

Upon consummation of the sale in August 2024, Royalty Pharma acquired 100% of the Vorasidenib Royalty Rights payments made by Servier on account of up to $1.0 billion in U.S. net sales for each calendar year. In addition, any such Vorasidenib Royalty Rights payments made by Servier on account of U.S. net sales in each calendar year in excess of $1.0 billion will be split, with Royalty Pharma having the rights to a 12% earn-out on those excess payments and Agios retaining the rights to a 3% earn-out on those excess payments, or the Retained Earn-Out Rights. As a result of the sale, we recognized income of $889.1 million ($905.0 million net of fees of $15.9 million) within the gain on sale of contingent payments line item in our consolidated statements of operations for the year ended December 31, 2024. Royalty income related to the Retained Earn-Out Rights, if any, will be recognized in the period when realizable.

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 focus on rare diseases. We are building 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; and expand our portfolio by advancing tebapivat, AG-181 and AG-236 and the rest of our preclinical pipeline as well as through disciplined business development aligned with our core therapeutic focus areas and capabilities.

Our Core Values

Our 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.

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.

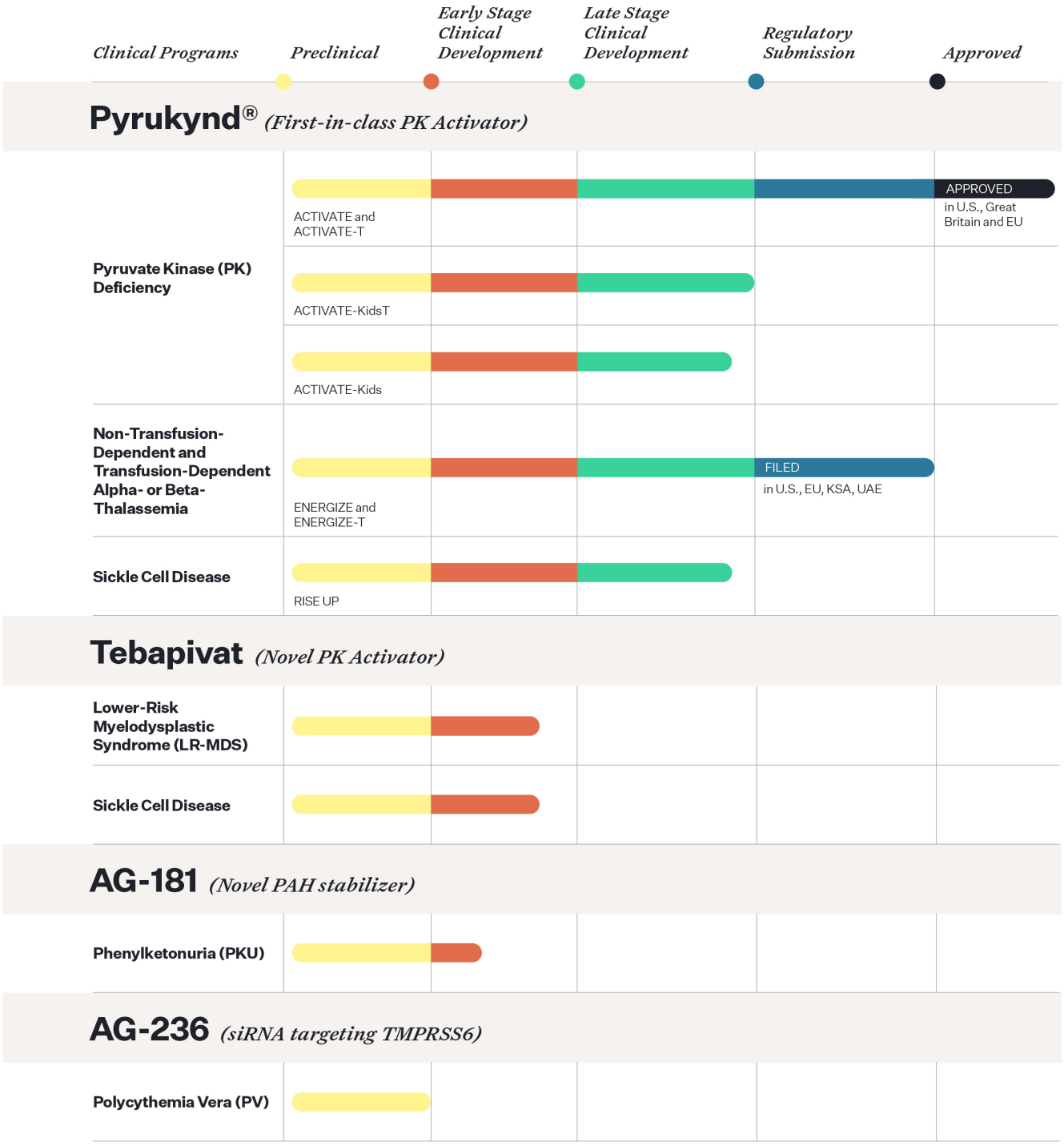
Classical hematology

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 Programs

PK is an enzyme involved 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 energy 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 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. We maintain a global registry, called Peak, for up to 500 adult and pediatric patients with PK deficiency 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, with approximately 6,000 diagnosed adults in the United States; approximately 70,000 individuals in Bahrain, Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates, also known as the Gulf Council Countries, or GCC; and greater than one million individuals worldwide. 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, splenectomy, iron chelation therapy and bone marrow transplantation, as well as recently approved therapies such as Reblozyl® (luspatercept-aamt) for the treatment of beta-thalassemia or Casgevy® and Zynteglo® for the treatment of transfusion-dependent beta-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)

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, approximately 150,000 individuals in the GCC, and greater than three million individuals worldwide. 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®, Casgevy®, and Lfygenia®. 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 (LR 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, or AML. The most common type of MDS is LR MDS, but many existing therapies and therapies under development focus on high risk MDS. Among patients with LR MDS, which accounts for approximately 70% of all MDS cases and are less likely to progress to AML, 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® and Rytelo® 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.

Other Programs

Phenylketonuria (PKU)

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 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.

Polycythemia Vera (PV)

PV is a rare blood disorder with no disease-modifying treatments that affects approximately 100,000 individuals in the United States. PV is characterized by excessive production of RBCs, which leads to increased blood volume and viscosity, and can result in thrombosis, cardiovascular events, enlarged spleen and death. Phlebotomy, which is the procedure of withdrawing blood, is the current standard of care for patients with PV.

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.

PYRUKYND® is approved for use by the FDA for the treatment of hemolytic anemia in adults with PK deficiency in the United States and by the European Commission for the treatment of PK deficiency in adult patients in the EU. Additionally, 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 December 2024, we announced that we submitted an sNDA to the FDA for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia, which was accepted with standard review by the FDA and granted a PDUFA goal date of September 7, 2025. Also in December 2024, we announced that we submitted an MAA to the EMA and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia. In addition, we are currently evaluating PYRUKYND® in clinical trials for the treatment of SCD and in pediatric patients with PK deficiency.

We have worldwide development and commercial rights to PYRUKYND®. In July 2024, we entered into a distribution agreement with NewBridge Pharmaceuticals FZ-LLC, or the NewBridge Agreement, pursuant to which we granted NewBridge the right to commercialize PYRUKYND® in the GCC region. We expect to fund the future development and commercialization costs related to this program. PYRUKYND® has been granted orphan drug designation for the treatment of PK deficiency by the FDA and the EMA. Additionally, PYRUKYND® has received orphan drug designation from the FDA for the treatment of thalassemia and SCD, orphan medicinal product designation from the EMA for the treatment of SCD, and breakthrough medicine designation from the Saudi Food and Drug Authority for the treatment of thalassemia.

We built our commercial infrastructure to support the commercialization of PYRUKYND® in adult PK deficiency in the United States, and have expanded this infrastructure to support the potential commercial launch of PYRUKYND® in thalassemia in the United States. In connection with our regulatory approvals in the EU and Great Britain, we are currently providing access to PYRUKYND® on a free of charge basis for eligible patients in those jurisdictions through a global managed access program. We provide access to PYRUKYND® for adult patients with PK deficiency in other jurisdictions upon request through the global managed access program, on either a free of charge or for charge basis. Our global managed access program has not had a significant impact on our business, financial condition or results of operations. 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, such as the NewBridge Agreement.

We are evaluating PYRUKYND® in numerous clinical trials, including the following:

- An extension study evaluating the long-term safety, tolerability and efficacy of treatment with PYRUKYND® in patients from ENERGIZE, our completed phase 3, double-blind, randomized, placebo-controlled multicenter study pivotal trial of PYRUKYND® in adults with non-transfusion-dependent alpha- or beta-thalassemia. We announced topline data for ENERGIZE in January 2024 and a more detailed analysis of the data in June 2024. A total of 194 patients were enrolled in the study, with 130 randomized to PYRUKYND® 100 mg twice-daily, or BID, and 64 randomized to matched placebo. 122 patients (93.8%) in the PYRUKYND® arm and 62 patients (96.9%) in the placebo arm completed the 24-week double-blind period of the study. The study met the primary endpoint of hemoglobin response, where treatment with PYRUKYND® demonstrated a statistically significant increase in hemoglobin response compared to placebo, as

42.3% of patients in the PYRUKYND® arm achieved a hemoglobin response, compared to 1.6% of patients in the placebo arm (2-sided p<0.0001). Treatment with PYRUKYND® also demonstrated statistically significant improvements compared to placebo for both key secondary endpoints: (i) change from baseline in average Functional Assessment of Chronic Illness Therapy-Fatigue, or FACIT-Fatigue, subscale score from week 12 to week 24 and (ii) change from baseline in average hemoglobin concentration from week 12 to week 24. During the 24-week double-blind period, four (3.1%) subjects in the PYRUKYND® arm experienced adverse events, or AEs, leading to discontinuation, and there were no AEs in the placebo arm leading to discontinuation. AEs that led to discontinuation in the PYRUKIND® arm were thrombocytopenia, arthralgia, abdominal distension, and 5 concurrent laboratory adverse events (alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increase, blood LDH increase, and international normalized ratio increase), all in one patient each.

- An extension study evaluating the long-term safety, tolerability and efficacy of treatment with PYRUKYND® in patients from ENERGIZE-T, our completed 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 alpha- or beta-thalassemia, defined as 6 to 20 red blood cell, or RBC, units transfused and ≤ six-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. We announced topline data for ENERGIZE-T in June 2024 and a more detailed analysis of the data in December 2024. A total of 258 patients were enrolled in the study, with 171 randomized to PYRUKYND® 100 mg twice-daily and 87 randomized to matched placebo. 155 patients (90.6%) in the PYRUKYND® arm and 83 patients (95.4%) in the placebo arm completed the 48-week double-blind period of the study. The study met the primary endpoint of transfusion reduction response, where treatment with PYRUKYND® demonstrated a statistically significant reduction in transfusion burden compared to placebo, as 30.4% of patients achieved a transfusion reduction response, compared to 12.6% of patients in the placebo arm (2-sided p=0.0003). Treatment with PYRUKYND® also demonstrated a statistically significant reduction in additional measures of transfusion reduction response compared to placebo as assessed by the three key secondary endpoints: (i) ≥50% reduction in transfused RBC units in any consecutive 24-week period through week 48 compared with baseline, (ii) ≥33% reduction in transfused RBC units from week 13 through week 48 compared with baseline, and (iii) ≥50% reduction in transfused RBC units from week 13 through week 48 compared with baseline. In addition, a higher proportion of patients in the PYRUKYND® arm (9.9%) compared to the placebo arm (1.1%) achieved the secondary endpoint of transfusion independence (transfusion-free for ≥8 consecutive weeks through week 48). The proportion of patients with any treatment-emergent adverse events, or TEAEs, was 90.1% in patients on PYRUKYND® and 83.5% in patients on placebo. The most frequent TEAEs that occurred in at least 10% of patients on PYRUKYND® were headache, upper respiratory tract infection, initial insomnia, diarrhea and fatigue. Serious TEAEs were reported in 11.0% and 15.3% of patients on PYRUKYND® and placebo, respectively; 2.3% and 1.2%, respectively, were considered treatment-related. During the 48-week double-blind period, 5.8% of the patients in the PYRUKYND® arm experienced a TEAE leading to discontinuation compared to 1.2% of patients in the placebo arm. The TEAEs leading to discontinuation of PYRUKYND®, each of which occurred in one patient, were diarrhea, paresthesia oral, concurrent anxiety and insomnia, initial insomnia, supraventricular tachycardia, fatigue, hypertransaminasemia, hepatitis C, hepatic cancer, and renal mass. The TEAE that led to discontinuation of the one patient on placebo was blood creatine phosphokinase increase.

  As indicated above, during the double-blind periods of ENERGIZE and ENERGIZE-T, two patients on PYRUKYND® experienced events of hepatocellular injury. In addition, during the open-label extension periods of both trials, a total of three patients experienced events of hepatocellular injury after switching from placebo to PYRUKYND®. All of these events occurred within the first six months of exposure to PYRUKYND® and liver tests improved following discontinuation of PYRUKYND®.

  Based on the results of the ENERGIZE and ENERGIZE-T trials, in December 2024 we announced that we filed regulatory applications for PYRUKYND® for the treatment of adult patients with non-transfusion-dependent and transfusion-dependent alpha- or beta-thalassemia with the FDA, EMA and Kingdom of Saudi Arabia and United Arab Emirates health authorities and we included in our regulatory applications hepatocellular injury as an important potential risk of PYRUKYND® in patients with thalassemia and proposed monthly monitoring of liver tests for the first six months of treatment with PYRUKYND®. We updated our PYRUKYND® clinical trial protocols across all indications to incorporate monthly monitoring of liver tests for the first six months of treatment and updated the U.S. Prescribing Information, or USPI, for PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency to reflect the aforementioned hepatocellular injury and monitoring.

- 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, or SCPCs, in the past 12 months, and have hemoglobin

within the range of 5.5 to 10.5 g/dL during screening. We enrolled 79 patients in the phase 2 portion of the trial, with 26 patients in the 50 mg twice daily mitapivat arm, 26 patients in the 100 mg twice daily mitapivat arm and 27 patients in the placebo arm. The primary endpoints of the phase 2 portion of the trial were hemoglobin response, defined as ≥ 1 g/dL increase in average hemoglobin concentration from week 10 to week 12 compared to baseline, and safety. In June 2023, we announced the phase 2 portion of this trial had achieved its primary endpoint of hemoglobin response in patients in both the 50 mg and 100 mg twice daily mitapivat arms. 46.2% of patients (n=12) in the 50 mg twice daily mitapivat arm and 50.0% of patients (n=13) in the 100 mg twice daily mitapivat arm achieved a hemoglobin response, compared to 3.7% of patients (n=1) in the placebo arm (2-sided p=0.0003 and 0.0001, respectively). In December 2023, we announced the following additional results of the phase 2 portion of the trial: (i) the least-squares mean (95% confidence interval) for average change from baseline in hemoglobin levels, from week 10 through week 12, for patients in the 50 mg twice daily mitapivat, 100 mg twice daily mitapivat, and placebo arms, respectively, was 1.11 (0.77, 1.45) g/dL, 1.13 (0.79, 1.47) g/dL, and 0.05 (−0.28, 0.39) g/dL; (ii) we observed improvements in annualized rates of SCPCs as the annualized rate of SCPCs (95% confidence interval) for patients in the 50 mg twice daily and 100 mg twice daily mitapivat arms, respectively, was 0.83 (0.34, 1.99) and 0.51 (0.16, 1.59), compared to 1.71 (0.95, 3.08) for patients in the placebo arm; (iii) we observed improvement in patient-reported fatigue scores in the 50 mg twice daily mitapivat arm compared to the placebo arm, and the least-squares mean (95% confidence interval) for average changes from baseline in patient-reported fatigue score, from week 10 through week 12, for patients in the 50 mg twice daily mitapivat, 100 mg twice daily mitapivat, and placebo arms, respectively, was −3.80 (−7.16, −0.45), −0.10 (−3.27, 3.08), and −0.17 (−3.40, 3.07). The safety profile for mitapivat observed in the phase 2 portion of the trial was generally consistent with previously reported data in other studies of SCD and other hemolytic anemias. The most common TEAEs in the 50 mg BID, 100 mg BID, and placebo arms, respectively, were: headache (n=6, 6, 7), arthralgia (n=3, 5, 9), dysmenorrhea (n=0, 3, 0), pain (n=3, 3, 2), pain in extremity (n=1, 3, 6), back pain (n=4, 2, 3), nausea (n=1, 2, 4), fatigue (n=4, 1, 5), and influenza-like illness (n=1, 1, 3). There were no serious TEAEs attributed to mitapivat and there were no AEs leading to drug reduction, discontinuation, interruption or death in either the mitapivat or the placebo arms. Of the 79 patients enrolled in the study, 73 continued into the Phase 2 open-label extension period. In October 2023, we enrolled the first patient in the phase 3 portion of this trial and we have since enrolled over 200 patients worldwide. 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 (100 mg twice daily) PYRUKYND® dose level or the placebo. The primary endpoints are hemoglobin response, defined as ≥1 g/dL increase in average hemoglobin from week 24 through week 52 compared to baseline, and annualized rate of SCPCs. The secondary endpoints include additional clinical efficacy measures related to anemia, hemolysis, erythropoiesis, patient-reported fatigue and pain, annualized frequency of hospitalizations for SCPCs, and change from baseline in six minute walk test. 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®. We have completed enrollment and expect to announce topline data for this trial in late 2025, with a potential U.S. commercial launch in 2026, if approved.

- 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.

  A total of 49 patients were enrolled in ACTIVATE-kidsT, with 32 randomized to mitapivat twice-daily and 17 randomized to matched placebo. 30 patients (93.8%) in the mitapivat arm and 16 (94.1%) in the placebo arm completed the 32-week double-blind period of the study. 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. We announced topline data for ACTIVATE-kidsT in August 2024. Using Bayesian methodology, the prespecified statistical criterion for the primary endpoint in ACTIVATE-kidsT was not met using low or moderate borrowing of data from the ACTIVATE-T study in adults. In the study, 28.1% of patients in the mitapivat arm achieved the primary endpoint of transfusion reduction response, compared to 11.8% of patients in the placebo arm. Transfusion-free response and normal hemoglobin response were secondary endpoints in this study and only observed in patients in the mitapivat arm. In the 32-week double-blind treatment period, mitapivat was generally safe and well-tolerated, with safety results consistent with the safety profile for mitapivat previously observed in adults with PK deficiency who are regularly transfused.

  A total of 30 patients were enrolled in ACTIVATE-kids, with 19 randomized to mitapivat twice-daily and 11 randomized to matched placebo. All patients in both treatment arms completed the 20-week double-blind period of the study. 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. We announced topline data for ACTIVATE-kids in February 2025. Using Bayesian methodology, the prespecified statistical criterion for the primary endpoint in ACTIVATE-kids was met using a range of relative borrowing from the adult ACTIVATE study, for all possible borrowing weights (ranging from 0 to 1). In addition, the pre-specified supportive analysis based on traditional methodology comparing the hemoglobin response

rate for mitapivat versus placebo provided further evidence that the primary endpoint was met. There were 31.6% of patients in the mitapivat arm achieving a hemoglobin response compared to 0% of patients in the placebo arm; the 95% confidence interval for the difference in hemoglobin response rates between mitapivat and placebo was >0 (95% CI=10.8% to 52.7%). In addition, improvements in changes from baseline for markers of hemolysis (indirect bilirubin, lactate dehydrogenase and haptoglobin) were observed in the mitapivat arm compared to the placebo arm. In the 20-week double-blind period of the study, a similar proportion of patients had AEs in the mitapivat and placebo arms and there were no discontinuations of study treatment due to AEs or for any reason. The safety results from the trial were consistent with the safety profile for mitapivat previously observed for adult patients with PK deficiency who are not regularly transfused.

- 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.

Tebapivat: Novel PK Activator

We are developing tebapivat, a novel PK activator for the potential treatment of LR MDS and hemolytic anemias. Tebapivat has been granted orphan drug designation for the treatment of MDS by the FDA.

We have completed a phase 1 clinical trial evaluating tebapivat in healthy volunteers and patients with SCD, and we expect to dose the first patient in a phase 2 clinical trial of tebapivat in adult patients with SCD in mid-2025.

We also initiated a phase 2a clinical trial of tebapivat in adults with LR MDS in the third quarter of 2022, and the trial has completed enrollment with 22 patients, including 12 patients classified as non-transfused and 10 patients classified as low transfusion burden. Patients received 5 mg of tebapivat once daily for up to 16 weeks. The two primary endpoints of the trial were transfusion independence (for patients classified as low transfusion burden), defined as transfusion-free for ≥ eight consecutive weeks during the 16-week treatment period, and hemoglobin response, defined as a ≥ 1.5 g/dL increase from baseline in the average hemoglobin concentration measured from week 8 through week 16.

In November 2023, we announced that we achieved clinical proof-of-concept in the phase 2a portion of the trial. We observed that four of the 10 patients with low transfusion burden achieved the transfusion independence endpoint, and one of the 22 patients achieved the hemoglobin response endpoint in the 16-week treatment period. The safety profile observed was consistent with data reported in the healthy volunteer study of tebapivat. 19 patients elected to enroll in the extension period for up to 156 weeks. We evaluated the phase 2a trial results and assessed the impact of those results on the phase 2b portion of the protocol, and based on the data generated in the phase 2a portion of the trial, we plan to increase the dosage levels evaluated in the phase 2b portion of the trial, which we initiated in the third quarter of 2024. We expect to complete enrollment in this phase 2b trial in late 2025.

Other Programs

In addition to the aforementioned development programs, we are developing AG-181, a PAH stabilizer for the potential treatment of PKU, for which we filed an IND in December 2023. We initiated a phase 1 clinical trial of AG-181 in healthy volunteers in the first quarter of 2024. Also, in July 2023, we entered into a license agreement with Alnylam for the development and commercialization of products containing or comprised of an siRNA preclinical development candidate discovered by Alnylam and targeting the TMPRSS6 gene, and we have begun preclinical development of a product candidate, AG-236, for the potential treatment of patients with PV. We expect to file an investigational new drug application, or IND, with the FDA for AG-236 for the treatment of PV in mid-2025.

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 United States 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, in-licensing opportunities 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®, tebapivat and AG-181, in addition to related compounds and potential back-up compounds, in an effort to establish intellectual property positions to protect these new chemical entities and methods of using these compounds in the treatment of diseases, as well as formulations, solid state forms, and manufacturing processes for these compounds. 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 tebapivat, as well as various solid state forms, methods of use and methods of manufacture for tebapivat and other novel compounds. As of February 1, 2025, we owned 17 issued United States patents and 434 issued foreign patents, and have pending patent applications in the United States and in various foreign jurisdictions. The patents that have issued or may issue for PYRUKYND® will have a statutory expiration date of at least 2030 to 2042, and the patents that have issued or may issue for tebapivat will have a statutory expiration date of at least 2038 to 2045. Patent term adjustments or patent term extensions could result in later expiration dates. In some cases, the term of a United States 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. We have issued patents and pending patent applications pertaining to our products/product candidates in our PK activator program in a number of foreign 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 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. We are also currently involved in adversarial proceedings before the European Patent Office. Two of the European patents in our PYRUKYND® portfolio, neither being the primary compound patent, have been challenged in opposition proceedings.

PAH stabilizer program

The patent portfolio for our PAH stabilizer program contains issued patents and pending patent applications directed to compositions of matter and methods of use for AG-181 and other novel PAH stabilizers. As of February 1, 2025, we owned one issued United States patent and two issued foreign patents and have pending patent applications in the United States and in various foreign jurisdictions. The patents that have issued or may issue for our PAH stabilizer program will have a statutory expiration date of at least 2043 to 2044. Patent term adjustments or patent term extensions could result in later expiration dates. In some cases, the term of a United States 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. We have issued patents and pending patent applications pertaining to our products/product candidates in our PAH stabilizer program in a number of foreign jurisdictions, including Argentina, Australia, Brazil, Canada, China, Europe, Japan, Lebanon, Mexico, Eurasia, Saudi Arabia, and Taiwan. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination 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 United States Patent and Trademark Office, or 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 product candidate and other factors. There can be no assurance that any of our pending patent applications will be issued 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. Nevertheless, confidential information and know-how can be difficult to protect. In particular, we anticipate that at least some of our technical information and know-how will, over time, become known within the industry through independent development, the publication of journal articles, 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 pharmaceutical, biotechnology and other related markets that address rare diseases, particularly hemolytic anemias, PKU and PV. There are other companies working to develop rare disease therapies, including divisions of large pharmaceutical companies and biotechnology companies of various sizes.

Our competitors include but are not limited to: BioMarin Pharmaceutical, Inc., or BioMarin; bluebird bio, Inc., or bluebird; Bristol-Myers Squibb Company, or BMS; CRISPR Therapeutics AG, or CRISPR; Emmaus Life Sciences, Inc., or Emmaus; Fulcrum Therapeutics, Inc., or Fulcrum; Geron Corporation, or Geron; Incyte Corporation, or Incyte; Ionis Pharmaceuticals, Inc., or Ionis; Merck & Co., Inc., or Merck; Novartis International AG, or Novartis; Novo Nordisk A/S, or Novo; Otsuka Pharmaceutical Co., Ltd., or Otsuka; Pfizer, Inc., or Pfizer; PharmaEssentia USA Corporation, or PharmaEssentia; Protagonist Therapeutics, Inc., or Protagonist, in collaboration with Takeda, Pharmaceutical Company Limited, or Takeda; PTC Therapeutics, Inc., or PTC; Rocket Pharmaceuticals, Inc., or Rocket Pharma; Silence Therapeutics plc, or Silence; Takeda; and Vertex Pharmaceuticals Incorporated, or Vertex.

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, phlebotomies, stem cell transplant and ERTs and there are several marketed therapies available for treating patients with hemolytic anemias, PKU and PV. For example, recently approved treatments for thalassemia, SCD, LR MDS, PKU and PV include Reblozyl® from Merck/BMS (formerly Acceleron/BMS); Revlimid® from BMS; Zynteglo® and Lyfgenia® from bluebird; Adakveo® from Novartis; Casgevy® from Vertex/CRISPR; Kuvan® and Palynziq® from BioMarin; Endari® from Emmaus; Besremi® from PharmaEssentia; Jakafi® from Incyte; and Rytelo® from Geron. 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 several products that are either small molecules, biologics, ERTs or gene therapies in various stages of development to treat hemolytic anemias, PKU and PV. 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 SCD; Pfizer is developing inclacumab and osivelotor (GBT-601) for the treatment of SCD; Fulcrum is developing

pociredir (FTX-6058) in SCD; Takeda is developing TAK-226 for the treatment of anemia in LR MDS; a number of companies, including PTC and Otsuka are developing therapies to treat PKU; and a number of companies, including Silence, Protagonist with Takeda, Italfarmaco S.p.A., Disc Medicine, Inc., Merck & Co., Inc., and Ionis are developing therapies to treat PV. These products may provide efficacy, safety, convenience and other benefits not provided by current marketed therapies or the current standards of care. 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 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 generic medicines currently on the market for 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®, tebapivat, and AG-181 are organic compounds of low molecular weight, generally called small molecules, and are dosed orally. Our siRNA program, AG-236, targeting the TMPRSS6 gene is an oligonucleotide intended for use as a sterile parenteral administration. Each can be manufactured in reliable and reproducible synthetic processes from readily available starting materials. The chemistries are amenable to scale-up and do not require unusual equipment in the manufacturing process. We expect to continue to develop product 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 in-house 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®, tebapivat, AG-181 and AG-236 for our ongoing and planned clinical testing and ongoing preclinical 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 multi-faceted 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.

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 responsible for initiating and managing 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 an NDA, or a sNDA for a change to a previously approved drug product, which submissions include 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 pursuant to PDUFA;
- approval of an NDA for the new drug product authorizing marketing of the new drug product for particular indications in the United States; 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 and 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. With passage of the FDA's Modernization Act 2.0 in December 2022, Congress eliminated provisions in both the FDCA and the Public Health Service Act, or PHSA, that required animal testing in support of an NDA. While animal testing may still be conducted, the FDA was authorized to rely on alternative non-clinical tests, including cell-based assays, microphysiological systems or bioprinted or computer models.

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 addition to reviewing an IND to assure the safety and rights of patients, the FDA also focuses on the quality of the investigation and whether it will be adequate to permit an evaluation of the drug's safety and efficacy. 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 trial 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 trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements, including GCP requirements, of the FDA 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 monitoring committee, or DMC. The DMC provides authorization as to whether or not a trial may move forward at designated check points based on access that only the DMC 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 PHSA, 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 National Institutes of Health. 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. The PHSA grants the Secretary of Health and Human Services, or HHS, the authority to issue a notice of noncompliance to a responsible party to failure to submit clinical trial information as required. The responsible party, however, is allowed 30 days to correct the noncompliance and submit the required information. As of December 19, 2024, the FDA has issued six notices of non-compliance, signaling the government’s willingness to enforce these requirements against non-compliant clinical trial sponsors. While these notices of non-compliance did not result in civil monetary penalties, the failure to submit clinical trial information to clinicaltrials.gov is 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 AEs, 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 AEs 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 December 2022, with the passage of the Food and Drug Omnibus Reform Act, or FDORA, Congress required sponsors to develop and submit a diversity action plan for each Phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, action plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on diversity action plans. In June 2024, the FDA issued draft guidance outlining the general requirements for diversity action plans. Unlike most guidance documents issued by the FDA, the diversity action plan guidance, when finalized, will have the force of the law because FDORA specifically dictates that the form and manner for submission of diversity action plans are specified in FDA guidance. In January 2025, in response to an executive

order issued by President Trump on Diversity, Equity and Inclusion programs, the FDA removed this draft guidance from its website. The implications of this action are not yet known.

In June 2023, the FDA issued draft guidance with updated recommendations for GCPs aimed at modernizing the design and conduct of clinical trials. The updates are intended to help pave the way for more efficient clinical trials to facilitate the development of medical products. The draft guidance is adopted from the International Council for Harmonisation's recently updated E6(R3) draft guideline that was developed to enable the incorporation of rapidly developing technological and methodological innovations into the clinical trial enterprise. In addition, the FDA issued draft guidance outlining recommendations for the implementation of decentralized clinical trials.

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 annually to the FDA within 60 days of the anniversary date that the IND went into effect and more frequently if serious AEs occur. These reports must include a development safety update report. 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.

Interactions with the FDA During the Clinical Development Program

Following the clearance of an IND and the commencement of clinical trials, a sponsor will continue to have interactions with the FDA and the sponsor may meet with the FDA at certain points in the clinical development program. Specifically, sponsors may meet with the FDA prior to the submission of an IND, or a pre-IND meeting, at the end of Phase 2 clinical trial, or an EOP2 meeting, and before an NDA is submitted, or a pre-NDA meeting. Meetings at other times may also be requested. These meetings provide an opportunity for the sponsor to share information about the data gathered to date with the FDA and for the FDA to provide advice on the next phase of development.

There are five types of meetings that occur between sponsors and the FDA. Type A meetings are those necessary for an otherwise stalled product development program to proceed or to address an important safety issue. Type B meetings include pre-IND and pre-NDA meetings as well as end of phase meetings, such as EOP2 meetings. A Type C meeting is any meeting other than a Type A or Type B meeting regarding the development and review of a product, including, for example, meetings to facilitate early consultations on the use of a biomarker as a new surrogate endpoint that has never been previously used as the primary basis for product approval in the proposed context of use. A Type D meeting is focused on a narrow set of issues (typically limited to no more than two focused topics) and should not require input from more than three disciplines or divisions. Finally, INitial Targeted Engagement for Regulatory Advice on CBER products, or INTERACT, meetings are intended for novel products and development programs that present unique challenges in the early development of an investigational product.

Such meetings may be conducted in person, via teleconference/videoconference, or written response only with minutes reflecting the questions that the sponsor posed to the FDA and the FDA's responses. The FDA has indicated that its responses, as conveyed in meeting minutes and advice letters, only constitute mere recommendations and/or advice made to a sponsor and, as such, sponsors are not bound by such recommendations and/or advice. Nonetheless, from a practical perspective, a sponsor's failure to follow the FDA's recommendations for design of a clinical program may put the program at significant risk of failure. In September 2023, the FDA issued draft guidance outlining the terms of such meetings in more detail.

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 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 the 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. In May 2023, the FDA issued new draft guidance that further describes the pediatric study requirements under PREA.

Filing and Review of an NDA

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 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 2025 is approximately $4.31 million. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2025 is $403,889 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. In the event that the FDA determines that an application does not satisfy this standard, it will issue a Refusal to File determination to the sponsor. 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 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.

A sponsor is required to submit a sNDA if it wishes to make a change to a product that has already been approved under an NDA. Such changes may include a revision of the labeling for the approved product, addition of a new indication, a change in the dosage, strength or formulation of the drug product, or a modification of the manner in which the drug is manufactured. Under the timelines established pursuant to PDUFA, the standard review time for an sNDA is generally 10 months from receipt of the application by the FDA.

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 comply with cGMP requirements and are 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.

Moreover, the FDA will review a sponsor's financial relationship with the principal investigators who conducted the clinical trials in support of the NDA. That is because, under certain circumstances, principal investigators at a clinical trial site may also serve as scientific advisors or consultants to a sponsor and receive compensation in connection with such services. Depending on the level of that compensation and any other financial interest a principal investigator may have in a sponsor, the sponsor may be required to report these relationships to the FDA. The FDA will then evaluate that financial relationship and determine whether it creates a conflict of interest or otherwise affects the interpretation of the trial or the integrity of the data generated at the principal investigator's clinical trial site. If so, the FDA may exclude data from the clinical trial site in connection with its determination of safety and efficacy of the investigational product.

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 called 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, either 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.

With the passage of FDORA in December 2022, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to: (i) require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded, (ii) require a sponsor of a product granted accelerated approval to submit progress reports on its post-approval studies to the FDA every six months until the study is completed; and (iii) use expedited procedures to withdraw accelerated approval of an NDA or biologics license application if certain conditions are not met, including where a confirmatory trial fails to verify the product's clinical benefit or where evidence demonstrates the product is not shown to be safe or effective under the conditions of use. The FDA may also use such procedures to withdraw an accelerated approval if a sponsor fails to conduct any required post-approval trial of the product with due diligence, including with respect to "conditions specified by the Secretary." The new procedures include the provision of due notice and an explanation for a proposed withdrawal, and opportunities for a meeting with the FDA Commissioner or the Commissioner's designee and a written appeal, among other things.

In March 2023, the FDA issued draft guidance that outlines its views and approach to accelerated approval. The FDA indicated that the accelerated approval pathway is commonly used for approval of oncology drugs due to the serious and life-threatening nature of cancer. Although single-arm trials have been commonly used to support accelerated approval, a randomized controlled trial is the preferred approach, as it provides a more robust efficacy and safety assessment and allows for direct comparisons to an available therapy. To that end, the FDA outlined considerations for designing, conducting, and analyzing data for trials intended to support accelerated approvals of oncology therapeutics. Subsequently, in December 2024 and January 2025, the FDA issued additional draft guidance relating to accelerated approval. This guidance describes the FDA's views on what it means to conduct a confirmatory trial with due diligence and how the agency plans to interpret whether such a study needs to be underway at the time of approval. While this guidance is currently only in draft form and will ultimately not be legally binding even when finalized, sponsors typically observe the FDA's guidance closely to ensure that their investigational products qualify for accelerated approval.

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 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 FDA will consider in determining the intended use of a drug or biologic. Moreover, with passage of the Pre-Approval Information Exchange Act in December 2022, sponsors of products that have not been approved may proactively communicate to payors certain information about products in development to help expedite patient access upon product approval. In addition, in January 2025, the FDA published final guidance outlining its policies governing the distribution of scientific information on unapproved uses of approved products to healthcare providers. The final guidance calls for such communications to be truthful, non-misleading, and scientifically sound and to include all information necessary for healthcare providers to interpret the strengths and weaknesses and validity and utility of the information about the unapproved use of the approved product. If a company engages in such communications consistent with the guidance's recommendations, the FDA indicated that it will not treat such communications as evidence of unlawful promotion of a new intended use for the approved product. While this guidance only applies to communications about unapproved uses of approved products, it may be helpful in understanding the FDA's approach to communications about unapproved products.

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 Department of Justice, or the DOJ, or the Office of the Inspector General of the

Department of HHS, 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. Manufacturers are required to have such systems and processes in place to comply with the DSCSA, but, so as not to disrupt supply chains, the FDA has granted certain exemptions from enhanced drug distribution security requirements for eligible trading partners for particular periods of time.

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 efficacy 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 studies or clinical trials 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

The Hatch-Waxman Amendments to the FDCA authorize 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 regulatory 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 regulatory exclusivity if the NDA includes reports of one or more new clinical trials, 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 trial 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 trials 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 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 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.

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 trial 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 patent term 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 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 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 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 several 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, or MDRP, 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 MDRP 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 point-of-sale-discount (currently 70%) 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 now remain in effect for six months into 2032.

The Consolidated Appropriations Act, which was signed into law by President Biden in December 2022, made several changes to sequestration of the Medicare program. Section 1001 of the Consolidated Appropriations Act delays the 4% Statutory Pay-As-You-Go Act of 2010, or PAYGO, sequester for two years, through the end of 2024. Triggered by enactment of the American Rescue Plan Act of 2021, the 4% cut to the Medicare program would have taken effect in January 2023. The Consolidated Appropriations Act's health care offset title includes Section 4163, which extends the 2% Budget Control Act of 2011 Medicare sequester for six months into 2032 and lowers the payment reduction percentages in years 2030 and 2031.

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 June 17, 2021, the Supreme Court dismissed the most recent judicial challenge to the ACA 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.

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, the Trump Administration 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 addition, the HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program to import certain prescription drugs from Canada into the United States. That regulation was challenged in a lawsuit by the Pharmaceutical Research and Manufacturers of America, or PhRMA, but the case was dismissed by a federal district court in February 2023 after the court found that PhRMA did not have standing to sue HHS. Several states have passed legislation establishing workgroups to examine the impact of a state importation program. Several other states have passed laws allowing for the importation of drugs from Canada. Certain of these states have submitted Section 804 Importation Program proposals to the FDA. On January 5, 2024, the FDA approved Florida's plan for Canadian drug importation. Florida now has authority to import certain products from Canada for a period of two years once certain conditions are met. Florida will first need to submit a pre-import request for each product selected for importation, which must be approved by the FDA. Florida will also need to relabel the products and perform quality testing of the products to meet FDA standards.

Further, 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 final rule would also eliminate the current safe harbor for Medicare drug rebates and create new safe harbors for beneficiary point-of-sale discounts and pharmacy benefit manager service fees. It originally was set to go into effect on January 1, 2022, but with passage of the Inflation Reduction Act of 2022, or IRA, has been delayed by Congress to January 1, 2032.

The IRA 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 $2,000 beginning in 2025.

On August 15, 2024, HHS published the results of the first Medicare drug price negotiations for ten selected drugs that treat a range of conditions, including diabetes, chronic kidney disease and rheumatoid arthritis. The prices of these ten drugs will become effective January 1, 2026. On January 17, 2025, CMS announced the selection of 15 additional drugs covered by Medicare Part D for the second cycle of negotiations. This second cycle of negotiations with participating drug companies will occur during 2025, and any negotiated prices for this second set of drugs will be effective starting January 1, 2027. CMS issued a public statement on January 29, 2025, declaring that lowering the cost of prescription drugs is a top priority of the new administration and CMS is committed to considering opportunities to bring greater transparency in the negotiation program.

The IRA includes a provision exempting orphan drugs from Medicare price negotiation but this exclusion has been interpreted by CMS in final guidance issued in July 2023 to apply only to those orphan drugs with an approved indication (or indications) for a single rare disease or condition. The final guidance clarifies that CMS will consider only active designations/approvals when evaluating a drug for the exclusion, such that designations/indications withdrawn before the selected drug publication date will not be considered. CMS also clarified that, if a drug loses its orphan drug exclusion status, the agency will use the earliest date of approval/licensure to determine whether the product is a qualifying single source drug subject to price negotiations.

In June 2023, Merck filed a lawsuit against HHS and CMS asserting that, among other things, the IRA's Drug Price Negotiation Program for Medicare constitutes an uncompensated taking in violation of the Fifth Amendment of the Constitution. Subsequently, several other parties, including the U.S. Chamber of Commerce and pharmaceutical companies, also filed lawsuits in various courts with similar constitutional claims against HHS and CMS. HHS has generally won the substantive disputes in these cases, and various federal district court judges have expressed skepticism regarding the merits of the legal arguments being pursued by the pharmaceutical industry. Certain of these cases are now on appeal, and, on October 30, 2024, the Court of Appeals for the Third Circuit heard oral argument in these cases. Litigation involving these and other provisions of the IRA will continue with unpredictable and uncertain results.

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. Many states have 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.

Federal and State Data Privacy Laws

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. If a sponsor fails to comply with applicable privacy laws, including applicable HIPAA privacy and security standards, it 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.

In addition to potential enforcement by the HHS, a sponsor is also potentially subject to privacy enforcement from the Federal Trade Commission, or FTC. The FTC has been particularly focused on the unpermitted processing of health and genetic data through its recent enforcement actions and is expanding the types of privacy violations that it interprets to be "unfair" under Section 5 of the FTC Act, as well as the types of activities it views to trigger the Health Breach Notification Rule (which the FTC also has the authority to enforce). The agency is also in the process of developing rules related to commercial surveillance and data security. Sponsors will need to account for the FTC's evolving rules and guidance for proper privacy and data security practices in order to mitigate risk for a potential enforcement action, which may be costly.

A number of states have passed comprehensive privacy laws, which are either in effect or will go into effect sometime over the next several years. These laws create obligations related to the processing of personal information, as well as special obligations for the processing of "sensitive" data, which includes health data in some cases. Some of the provisions of these laws may apply to our business activities. Other states are or will be considering similar laws in the future, and Congress has also been debating passing a federal privacy law. There are also states that are specifically regulating health information that may affect our business. 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.

Plaintiffs' lawyers are also increasingly using privacy-related statutes at both the state and federal level to bring lawsuits against companies for their data-related practices. In particular, there have been a significant number of cases filed against companies for their use of pixels and other web trackers. These cases often allege violations of the California Invasion of Privacy Act and other state laws regulating wiretapping, as well as the federal Video Privacy Protection Act.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a sponsor 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 MAA and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Preclinical Studies

Non-clinical studies are performed to demonstrate the health or environmental safety of new chemical or biological substances. Non-clinical (pharmaco-toxicological) studies must be conducted in compliance with GLP principles as set forth in EU Directive 2004/10/EC (unless otherwise justified for certain particular medicinal products – e.g., radio-pharmaceutical precursors for radio-labeling purposes). In particular, non-clinical studies, both *in vitro* and *in vivo*, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organisation for Economic Co-operation and Development requirements.

Clinical Trial Approval

Under the Clinical Trials Regulation (EU) No 536/2014, or the Clinical Trials Regulation, the sponsor of a clinical trial to be conducted in more than one Member State of the EU, or EU Member State, is only required to submit a single application for approval.

Sponsors must also obtain prior approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the sponsor may only start a clinical trial at a specific clinical site after the applicable ethics committee has issued a favorable opinion.

As of January 31, 2025, all clinical trials (including those which are ongoing) are subject to the provisions of the Clinical Trials Regulation.

Parties conducting certain clinical trials must, as in the United States, post clinical trial information in the EU at the EudraCT website.

Priority Medicines (PRIME) Designation in the EU

The EMA has implemented the priority medicines, or PRIME, scheme which 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 MAA 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; 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 trials, 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.

Exceptional Circumstances

A marketing authorization may also be granted "under exceptional circumstances" when the applicant can show that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use even after the product has been authorized and subject to specific procedures being introduced. This may arise in particular when the intended indications are very rare and, in the present state of scientific knowledge, it is not possible to provide comprehensive information, or when generating data may be contrary to generally accepted ethical principles. This marketing authorization is similar to the conditional marketing authorization, as it is reserved for medicinal products to be approved for severe diseases or unmet medical needs and the applicant does not hold the complete data set legally required for the grant of a marketing authorization. However, unlike the conditional marketing authorization, the applicant does not have to provide the missing data and will never have to. Although the marketing authorization "under exceptional circumstances" is granted definitively, the risk-benefit balance of the medicinal product is reviewed annually and the marketing authorization is withdrawn in case the risk-benefit ratio is no longer favorable. Under these procedures, before granting the marketing authorization, the EMA or the competent authorities of the member states make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety, and efficacy. Except conditional marketing authorizations, marketing authorizations have an initial duration of five years. After these five years, the authorization may be renewed on the basis of a reevaluation of the risk-benefit balance.

Regulatory Data Protection in the EU

In the EU, innovative medicinal products approved based on 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.

The EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative. The European Commission's proposal for revision of several legislative instruments related to medicinal products was published in April 2023 and includes, among other things, provisions that would potentially reduce the duration of regulatory data protection. The European Parliament requested several amendments in April 2024. At this time, the proposed revisions remain to be agreed and adopted by the European Parliament and European Council and the proposals may therefore be substantially revised before adoption, which is not anticipated before early 2026. The revisions may, however, have a significant impact on the pharmaceutical industry in the long term, if and when adopted.

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 based on 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 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 is 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 10,000 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 15 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

Many countries outside of the United States maintain rigorous laws governing the privacy and security of personal information. 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 subject to the GDPR. 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 EEA, including the United States, permits data protection authorities to impose large penalties for violations of the GDPR, and 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. 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. There are ongoing concerns about the ability of companies to transfer personal data from the EU to other countries.

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

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 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, 2024, we had 486 full-time employees and 2 part-time employees, all based in the United States and of which 114 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 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 adopted a pay for performance philosophy and provide a competitive and balanced compensation and benefits package, including short-term and long-term incentives, a 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 set goals and track our progress to ensure that we continue to incorporate different voices across the business. 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 are a majority female organization and maintain significant representation at all levels, including the Board of Directors. As of December 31, 2024, 60% of our workforce were women. Racial and ethnic diversity continues to be an area of focus at the Company. As of December 31, 2024, 35% of our workforce were ethnically diverse and 41% of all new hires that joined the Company in 2024 were ethnically diverse. 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. We received feedback from employees that helped inform how we approach programs and opportunities to improve the employee experience heading into 2024. 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 the industry average.

We are committed to providing employees with an opportunity to choose the right working arrangement for them based on their role: whether remote, hybrid, or 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 2024, 85% of our new hires chose to work remotely and our overall organization continues to have a majority population working in a remote capacity representing 66% of all employees.

We believe our ability to evolve with the ever-changing environment, coupled with our long-standing culture and values around flexibility and connection, continue to help 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 Annual Report on 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 and People Committee, Nominating and Corporate Governance Committee, and Science and Technology 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.

PYRUKYND® (mitapivat) is approved for use by the FDA for the treatment of hemolytic anemia in adults with PK deficiency in the United States and by the European Commission for the treatment of PK deficiency in adult patients in the EU. Additionally, 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 December 2024, we announced that we submitted an sNDA, to the FDA for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia, which was accepted with standard review and granted a PDUFA goal date of September 7, 2025. Also in December 2024, we announced that we submitted a MAA to the EMA, and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia.

Our ability to generate meaningful revenue from PYRUKYND® will depend heavily on our successful development and commercialization of the product. We generated $36.5 million, $26.8 million and $11.7 million of net product revenues from sales of PYRUKYND® in the years ended December 31, 2024, 2023 and 2022, respectively. In connection with our regulatory approval in the EU and Great Britain, we are currently providing access to PYRUKYND® on a free of charge basis for eligible patients in those jurisdictions through a global managed access program. We provide access to PYRUKYND® for adult patients with PK deficiency in other jurisdictions upon request through the global managed access program, on either a free of charge or for charge basis. 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, such as the NewBridge Agreement.

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 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 and sustain commercial demand that results in expected sales of PYRUKYND®;
- PYRUKYND® becomes subject to unfavorable pricing regulations and third-party reimbursement practices;
- 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®;
- significant safety, manufacturing and/or quality risks are identified;
- PYRUKYND® fails 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 other indications.

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-stage product candidates, including the potential approval of PYRUKYND® for the treatment of thalassemia or SCD in the United States and in other jurisdictions. Clinical trials of our product candidates may not be successful for a number of important reasons. If we or our collaborators are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We have invested a significant portion of our efforts and financial resources in the identification of our product candidates and the development of our most advanced clinical programs, including PYRUKYND® and tebapivat. 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®. In December 2024, we announced that we submitted an sNDA to the FDA for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia, which was accepted with standard review and granted a PDUFA goal date of September 7, 2025. Also in December 2024, we announced that we submitted an MAA to the EMA and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia. We cannot be certain that we will obtain marketing approval of PYRUKYND® in thalassemia in such jurisdictions, nor can we be certain that we will obtain marketing approval of PYRUKYND® for any other indication or in other jurisdictions.

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 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 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 the addition of safety warnings, or it could result in the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. For example, in January 2025, the USPI for PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency was updated to include information regarding hepatocellular injury observed in clinical trials in patients with thalassemia treated with PYRUKYND® at a higher dose than recommended for patients with PK deficiency;
- 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 failing 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® or tebapivat, we cannot provide any assurances that there will not be other treatment-related severe adverse events in our other clinical trials, or that our other trials will not be placed on clinical hold in the future.

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, and 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 have and may in the future enter into additional 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. For example, in July 2023, we entered into a license agreement with Alnylam for the development and commercialization of products containing or comprised of an siRNA development candidate discovered by Alnylam and targeting the TMPRSS6 gene, and we have begun preclinical development of a product candidate for the potential treatment of patients with PV.

Our ability to successfully in-license or acquire assets and develop product candidates following such transactions is unproven. If we do identify additional 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. Such transactions may require us to relinquish rights to develop product candidates in certain indications, limit our ability to pursue certain targets or require us to make significant milestone or royalty payments to third parties upon achievement of certain events. For example, we are responsible to pay up to $130.0 million in potential development and regulatory milestones, in addition to sales milestones as well as tiered royalties on annual net sales, if any, of any licensed products, under the license agreement with Alnylam. Further, 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.

Public health epidemics or pandemics may affect our ability to initiate or continue our planned, ongoing and future preclinical studies and 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.

We may face delays, disruptions or shortages as a result of public health epidemics or pandemics that may affect our ability to initiate and complete preclinical studies and clinical trials or impact our commercialization efforts. We have previously experienced disruptions to certain clinical and research activities at our contract research organizations, or CROs, due to the COVID-19 pandemic. Any future pandemic or public health emergency could result in delays or pauses in site initiation, participant recruitment and enrollment, participant dosing, distribution of clinical trial materials, study monitoring and data analysis due to changes in hospital or university policies, federal, state or local regulations, diversion of hospital resources or other reasons related to a public health emergency. If a pandemic or public health emergency arises in the future, we may face difficulties recruiting or retaining patients in our ongoing clinical trials, and 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 may necessitate remote data verification. In addition, limitations on the ability to visit sites may 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 cannot be certain what the overall impact of future health emergencies or pandemics will be on our business.

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.

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;
- proximity and availability of clinical trial sites for prospective patients; and
- the impact of any health epidemics, pandemics or other contagious outbreaks or geopolitical events, such as war.

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.

Under the federal Food and Drug Omnibus Reform Act, or FDORA, sponsors are required to develop and submit a diversity action plan for each phase 3 clinical trial or any other "pivotal study" of a new drug product. These plans are meant to encourage enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. In June 2024, as mandated by FDORA, the FDA issued draft guidance outlining the general requirements for diversity action plans. Unlike most guidance documents issued by the FDA, the diversity action plan guidance when finalized will have the force of law. . In January 2025, in response to an executive order issued by President Trump on Diversity, Equity and Inclusion programs, the FDA removed this draft guidance from its website. The implications of this action are not yet known. If we are not able to adhere to any new requirements, our ability to conduct clinical trials may be delayed or halted.

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; Novo Nordisk A/S, or Novo Nordisk, and Pfizer Inc., or Pfizer, are developing molecules for the treatment of SCD; Fulcrum Therapeutics Inc., or Fulcrum, is developing a treatment for SCD; PTC Therapeutics, Inc., or PTC, and Otsuka Pharmaceutical Co., Ltd., or Otsuka, are developing therapies to treat PKU; and Protagonist Therapeutics, or Protagonist, with Takeda Pharmaceutical Company Limited, or Takeda, Ionis Pharmaceuticals, Inc., or Ionis, Silence Therapeutics, or Silence, Italfarmaco S.p.A., Disc Medicine, Inc., or Disc Medicine, and Merck & Co., Inc., or Merck, are developing therapies to treat PV. 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.

In addition, we have a small number of clinical trial sites for certain clinical trials in the Middle East, including in Lebanon and Israel, that could be affected by the current armed conflict in the region.

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, or result in increased development costs for our product candidates, which could have an adverse effect on our business, results of operations and financial condition.

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 positive results of completed 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 our 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. The results of clinical trials of PYRUKYND® for the treatment of PK deficiency and thalassemia are not predictive of results of our ongoing clinical trials of PYRUKYND® in other indications, such as SCD, and the results of our early-stage clinical trials of tebapivat are not predictive of our later stage clinical trial of tebapivat. 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.

Interim and preliminary data from clinical trials that we announce or publish from time to time may change as more patient data becomes available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may announce or publish interim or preliminary data from our clinical trials. Interim or preliminary data from clinical trials are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. We also make assumptions, estimations, calculations, and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully evaluate all data. Preliminary or interim data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we have previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Adverse differences between preliminary or interim data and final data could be material and could significantly harm our reputation and business prospects.

We conduct clinical trials at sites outside the United States. The FDA may not accept data from trials conducted in such locations, and the conduct of trials outside the United States could subject us to additional delays and expense.

We conduct and plan to conduct one or more clinical trials with one or more trial sites that are located outside the United States. The acceptance by the FDA or other regulatory authorities of study data from clinical trials conducted outside their jurisdiction may be subject to certain conditions or may not be accepted at all.

In addition, even where the foreign study data are not intended to serve as the sole basis for approval, the FDA will not accept the data as support for an application for marketing approval unless the study is well-designed and well-conducted in accordance with GCP requirements and the FDA is able to validate the data from the study through an onsite inspection if deemed necessary. Many foreign regulatory authorities have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA or any comparable foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA or any comparable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which could be costly and time-consuming, and may result in current or future product candidates that we may develop not receiving approval for commercialization in the applicable jurisdiction.

Conducting clinical trials outside the U.S. also exposes us to additional risks, including risks associated with:

- additional foreign regulatory requirements;
- foreign exchange fluctuations;
- compliance with foreign manufacturing, customs, shipment and storage requirements;
- cultural differences in medical practice and clinical research;
- diminished protection of intellectual property in some countries; and

- interruptions or delays in our trials resulting from geopolitical events, such as war or terrorism.

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 are prioritizing 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 2 trial in LR MDS, our phase 1 trial for AG-181, our PAH stabilizer for the potential treatment of PKU, and AG-236, our preclinical development of a product candidate for the potential treatment of patients with PV. 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 warnings on the product label;
- 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.

For example, in January 2025, the USPI for PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency was updated to include information regarding liver injury observed in patients with thalassemia treated with PYRUKYND® at a higher dose than recommended for patients with PK deficiency.

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 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 prevalence and severity of any side effects;
- 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 sales, marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- product labeling or product insert requirements of the FDA or other regulatory authorities, including any limitations or warnings contained in a product's approved labeling.

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 any of our product candidates if they are approved.

We have limited experience in the sale, marketing and distribution of pharmaceutical products. To achieve commercial success for approved medicines for which we retain sales and marketing responsibilities, we must either continue to develop our sales and marketing organization or outsource these functions to other third parties. We have established sales and marketing capabilities to support our commercialization of PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency in the United States. In addition, in connection with our regulatory approvals in the EU and Great Britain, we are currently providing access to PYRUKYND® free of charge for eligible patients in those jurisdictions through a global managed access program. We provide access to PYRUKYND® for adult patients with PK deficiency in other jurisdictions upon request through the global managed access program, on either a free of charge or for charge basis. 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, including the NewBridge Agreement.

We may need to further build our sales and marketing infrastructure, either directly or with third-party partners 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, 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 provide certain development estimates related to the development and regulatory approval of PYRUKYND® and our product candidates. If we do not achieve our projected development or regulatory approval estimates in the timeframes we announce and expect, the commercialization of our products may be delayed and, as a result, our stock price may decline.

From time to time, we provide estimates related to the development of PYRUKYND® and our product candidates. We also estimate the timing of the anticipated accomplishment of various scientific, preclinical, clinical, regulatory and other product development goals. These estimates may include the commencement or completion of clinical trials, the timing of completing

enrollment, the timing for reporting clinical trial results and the timing of submission of regulatory filings in various jurisdictions. From time to time, we may publicly announce our estimates, including the timing of certain milestones related to our product candidates. All of these estimates are and will be based on numerous assumptions. The actual results and timing of our preclinical studies, clinical trials and regulatory submissions can vary dramatically compared to our estimates, in some cases for reasons beyond our control. If our estimates change or we do not meet the timing of our estimates as publicly announced, or at all, the commercialization of our products may be delayed or never achieved and, as a result, our stock price may decline.

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 tebapivat and our other 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 may 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 indications for which we are developing our product or our product candidates, such as PK deficiency, thalassemia, SCD, LR MDS, PKU, and PV. For example, Merck and Bristol-Myers Squibb Company, or BMS, are marketing a therapy to treat beta thalassemia and LR MDS, and are conducting clinical trials for alpha thalassemia and LR MDS patients that are erythropoeisis-stimulating agent naïve and non-transfusion dependent; Geron Corporation recently announced FDA approval of a treatment for adults with LR MDS with transfusion-dependent anemia; Novartis International AG, or Novartis, and Emmaus Life Sciences are each marketing therapies to treat SCD; BioMarin Pharmaceutical Inc., or BioMarin, is marketing and conducting clinical trials for therapies to treat PKU; Pfizer is conducting clinical trials for therapies in SCD; Novo Nordisk is conducting clinical trials for the treatment of alpha and beta thalassemia and SCD; bluebird is marketing a gene therapy to treat transfusion-dependent beta-thalassemia and SCD; Vertex, with CRISPR, is marketing a gene therapy targeting SCD and transfusion-dependent beta-thalassemia; Fulcrum is conducting clinical trials for a potential treatment for SCD; PTC and Otsuka and are conducting clinical trials for potential treatments for PKU; PharmaEssentia Corp, or PharmaEssentia, and Incyte Corporation, or Incyte, are marketing therapies to treat PV, and Protagonist with Takeda, Ionis, Italfarmaco S.p.A., Disc Medicine, Merck, and Silence are developing therapies to treat PV; Rocket Pharma is developing a therapy for the treatment of PK deficiency; and a number of other biotechnology companies have product candidates in clinical development in similar indications as ours.

There are a variety of treatment options available, including a number of marketed enzyme replacement therapies, or ERTs, for treating patients with rare diseases. In addition to currently marketed therapies, there are also a number of products that are either ERTs, 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.

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 companies 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 regulatory 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 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-on-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 regulatory 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 trial 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 regulatory 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 things, 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 information technology systems, or those of any third parties with which we contract, may fail or suffer security breaches, loss of data or other disruptions which could result in a material disruption of our product development programs, compromise sensitive information related to our business or prevent us from accessing critical information, trigger legal obligations, potentially exposing us to liability, competitive or reputational harm or otherwise adversely affecting our business and financial results.

Despite the implementation of security measures, our internal information technology 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 or business partners, or from cyber incidents by malicious third parties. Cybersecurity incidents are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cybersecurity 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. Cybersecurity incidents also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. Attackers may use artificial intelligence and machine learning to launch more automated, targeted and coordinated attacks against targets. 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. We may not be able to anticipate all types of security threats, and we may not be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched, and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations or hostile foreign governments or agencies.

System failures, accidents, cybersecurity 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, and, as a result, 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 processes, systems and controls designed to prevent these events from occurring, and we have a process to assess, identify and manage 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 cannot guarantee that the measures we have taken to date, and actions we may take in the future, will be sufficient to prevent any cyber-attacks or security breaches.

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 and the EU. 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 the federal Health Insurance Portability and Accountability Act of 1996, or 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. Enforcement activity by the U.S. Department of Health & Human Services, or HHS, 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 addition to potential enforcement by HHS, we are also potentially subject to privacy enforcement from the Federal Trade Commission, or FTC. The FTC has been particularly focused on the unpermitted processing of health and genetic data through its recent enforcement actions and is expanding the types of privacy violations that it interprets to be "unfair" under Section 5 of the FTC Act of 1914, as well as the types of activities it views to trigger the Health Breach Notification Rule (which the FTC also has the authority to enforce). The agency is also in the process of developing rules related to commercial surveillance and data security that may impact our business. We will need to account for the FTC's evolving rules and guidance for proper privacy and data security practices in order to mitigate our risk for a potential enforcement action, which may be costly. If we are subject to a potential FTC enforcement action, we may be subject to a settlement order that requires us to adhere to very specific privacy and data security practices, which may impact our business. We may also be required to pay fines as part of a settlement (depending on the nature of the alleged violations). If we violate any consent order that we reach with the FTC, we may be subject to additional fines and compliance requirements.

A number of states have passed comprehensive privacy laws, which are either currently in effect or will go into effect sometime over the next several years. These laws create obligations related to the processing of personal information, as well as special obligations for the processing of "sensitive" data (which includes health data in some cases). Some of the provisions of these laws may apply to our business activities. There are also states that are strongly considering or are in the process of enacting privacy laws that will go into effect in 2025 and beyond. Other states will be considering these laws in the future, and Congress has also been debating passing a federal privacy law. There are also states that are specifically regulating health information that may affect our business. 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.

Plaintiffs' lawyers in the United States are also increasingly using privacy-related statutes at both the state and federal level to bring lawsuits against companies for their data-related practices. In particular, there have been a significant number of cases filed against companies for their use of pixels and other web trackers. These cases often allege violations of the California Invasion of Privacy Act and other state laws regulating wiretapping, as well as the federal Video Privacy Protection Act. The rise in these types of lawsuits creates potential risk for our business.

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 European Economic Area, or 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.

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 challenges as a smaller, less diversified company.

Following the sale of our oncology business to Servier in 2021, 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 that PYRUKYND® is not approved for thalassemia or SCD, the possibility of adverse clinical and other developments in respect of PYRUKYND®, tebapivat or our other product candidates, and unanticipated changes in applicable laws and regulations that may adversely affect the rare disease business.

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® for PK deficiency, 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, potential royalty payments with respect to annual U.S. net sales of vorasidenib in excess of $1.0 billion, or the Retained Earn-Out Rights, and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, 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 Retained Earn-Out Rights described above and we cannot be certain we will ever receive any payments as a result of the Retained Earn-Out Rights. 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, selling or licensing our assets, 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 fund our operating expenses and capital expenditures, 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. Our estimate as to what extent we expect our existing cash, cash equivalents, and marketable securities to be available to fund our operating expenses and capital expenditures 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 payments, if any, we may receive on account of the Retained Earn-Out Rights;
- the costs and timing of our ongoing and future commercialization activities, including product manufacturing, sales, marketing and distribution, for PYRUKYND® in the approved jurisdictions and for any product candidate for which we may receive approval;
- 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, including the amount and timing of future milestone and royalty payments payable to Alnylam pursuant to the license agreement;
- the costs, timing and outcome of regulatory review of our product candidates, including with respect to regulatory submissions for PYRUKYND® for the treatment of thalassemia;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- 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 public health epidemics; and
- operational delays, disruptions and/or increased costs associated with global economic and political developments, 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 income for the year ended December 31, 2024 was $673.7 million and our net loss for the year ended December 31, 2023 was $352.1 million. As of December 31, 2024, we had an accumulated deficit of $148.9 million. The net income we generated in the year ended December 31, 2024 was primarily due to the sale of the Vorasidenib Royalty Rights and our receipt of the Vorasidenib Milestone Payment. Prior to the sale of our oncology business to Servier in March 2021, 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. In December 2024, we announced that we submitted an sNDA to the FDA for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia, which was accepted with standard review by the FDA and granted a PDUFA goal date of September 7, 2025. Also in December 2024, we announced that we submitted a MAA to the EMA, and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia.

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, and we provide access to PYRUKYND® for adult patients with PK deficiency in other jurisdictions through the global managed access program on either a free of charge or for charge basis. 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, such as the NewBridge Agreement.

PYRUKYND® is the first product we have received marketing approval for following the sale of our oncology business. 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.

We expect to finance our operations primarily through cash on hand, potential royalty payments with respect to the Retained Earn-Out Rights, and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, we may pursue opportunistic debt offerings, and equity or equity-linked offerings. 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 and year to year. We anticipate that we will incur significant expenses if and as we:

- prepare for and 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; 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.

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. For example, the federal Tax Cuts and Jobs Act of 2017, or the Tax Act and the Inflation Reduction Act of 2022, or IRA, made significant changes to corporate taxation at the federal level. 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 the 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 or whether additional tax legislation could be passed in the future.

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 EEA 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 ongoing clinical, nonclinical, and preclinical programs.

If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, or 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 geopolitical events, 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 currently applicable regulations, or regulations or specifications to which we become subject in the future, 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.

In addition, we currently rely on foreign third-party manufacturers and/or CROs, including those in China, and will likely continue to rely on foreign third-party manufacturers and/or CROs in the future. Foreign third-party manufacturers and/or CROs may be subject to U.S. legislation, including sanctions, trade restrictions and other foreign regulatory requirements which could increase the cost or reduce the supply of material or services available to us, delay the procurement or supply of such material or services, or have an adverse effect on our ability to secure significant commitments from governments to purchase our potential therapies. Moreover, in September 2024, the U.S. House of Representatives passed the BIOSECURE Act (H.R. 7085) and the Senate has advanced a substantially similar bill (S.3558), which legislation, if passed and enacted into law, would restrict the ability of U.S. biopharmaceutical companies like us to purchase services or products from, or otherwise collaborate with, specifically named Chinese biotechnology companies and authorizes the U.S. government to impose such restrictions on entities transaction with additional Chinese biotechnology companies as a condition of U.S. government contract, grant, and loan funding. The legislation contains a grandfathering provision that would prevent disruption to the provision of services or products furnished under contracts with the targeted biotechnology companies entered before the effective date of the legislation until January 1, 2032. It is possible some of our contractual counterparties could be impacted by this legislation.

If either we or any third parties on which we rely are adversely impacted by restrictions resulting from the emergence of public health epidemics, by rising global energy costs or energy shortages or rationing and/or geopolitical events and the impacts of the Russia-Ukraine war, 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 active pharmaceutical ingredient 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, such as the NewBridge Agreement, 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. In addition, our ability to enter into arrangements with collaborators in specific regions, such as the Middle East, may be affected by localized geopolitical unrest or military conflict, such as the current armed conflict in the region.

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, CROs,

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.

The United States maintains 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, are 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, two of the European patents in our mitapivat portfolio, neither being the primary compound patent, have been challenged in opposition proceedings in the European Patent Office. The revocation of either of these European patents could potentially allow additional competitor drugs, if approved, to enter the European marketplace earlier than anticipated.

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, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, 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.

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.

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, supplemental NDA 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 CROs 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.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or a comparable foreign regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

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.

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. For example, 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, 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.

In addition, we could be adversely affected by several significant administrative law cases decided by the U.S. Supreme Court in 2024, including most notably, *Loper Bright Enterprises v. Raimondo*, which overruled the Supreme Court's previous ruling that courts defer to reasonable agency interpretations of statutes that are silent or ambiguous on a particular topic. The ruling requires courts to exercise their independent judgment when deciding whether an agency has acted within its statutory authority, and that courts may not defer to an agency interpretation solely because a statute is ambiguous. This decision and other administrative law cases may result in additional legal challenges to regulations and guidance issued by federal regulatory agencies, including the FDA and CMS, that we have relied on and intend to rely on in the future. Any such challenges, if successful, could have a material impact on our business. In addition to potential changes to regulations and agency guidance as a result of legal challenges, these decisions may result in increased regulatory uncertainty and delays in and other impacts to the agency rulemaking process, any of which could adversely impact our business and operations.

Additionally, our ability to develop and market new drug products may be impacted based on current or future litigation in the federal court system challenging the FDA’s approval of other companies' drugs. Depending on the outcome of this type of litigation, our ability to develop new drug product candidates and to maintain approval of existing drug products could be at risk and our efforts to develop and market new drug products could be delayed, undermined or subject to protracted litigation.

Finally, with the change in presidential administrations in 2025, there is substantial uncertainty as to how, if at all, the new administration will seek to modify or revise the requirements and policies of the FDA and other regulatory agencies with jurisdiction over our product candidates. The impending uncertainty could present new challenges or potential opportunities as we navigate the clinical development and approval process for our product candidates.

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 EU 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.

In addition, foreign regulatory authorities may change their approval policies and new regulations may be enacted. For instance, EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative. The European Commission’s proposal for revision of several legislative instruments related to medicinal products (including potentially reducing the duration of regulatory data protection and revising the eligibility for expedited

pathways) was published in April 2023, and the European Parliament has requested several amendments in April 2024. The proposed revisions remain to be agreed and adopted by the European Parliament and European Council and the proposals may therefore be substantially revised before adoption, which is not anticipated before early 2026. The revisions may, however, have a significant impact on the pharmaceutical industry and our business in the long term.

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 the E.U., 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 currently 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.

The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA or Congress 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 REMS.

The FDA and other agencies, including the Department of Justice, or 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 actions 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. Such laws and regulations include the federal Anti-Kickback Statue; the federal False Claims Act; HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act; the federal Physician Payments Sunshine Act; and analogous state and foreign laws and regulations.

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 member states of the EU, or the 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 built our commercial infrastructure to support the commercialization of PYRUKYND® in adult PK deficiency in the United States, and have expanded this infrastructure to support the potential commercial launch of PYRUKYND® in thalassemia 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, and we provide access to PYRUKYND® for adult patients with PK deficiency in other jurisdictions through the global managed access program on either a free of charge or for charge basis. 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 candidate for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, 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 for six months into fiscal year 2032. 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.

Indeed, under current legislation, the actual reductions in Medicare payments may vary up to 4%. The Consolidated Appropriations Act, which was signed into law by President Biden in December 2022, made several changes to sequestration of the Medicare program. Section 1001 of the Consolidated Appropriations Act delays the 4% Statutory Pay-As-You-Go Act of 2010 sequester for two years, through the end of calendar year 2024. Triggered by enactment of the American Rescue Plan Act of 2021, the 4% cut to the Medicare program would have taken effect in January 2023. The Consolidated Appropriations Act's health care offset title includes Section 4163, which extends the 2% Budget Control Act of 2011 Medicare sequester for six months into fiscal year 2032 and lowers the payment reduction percentages in fiscal years 2030 and 2031.

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 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 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.

We cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition.

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. In markets outside of the United States and the EU, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In many countries, including those of the EU, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we or our collaborators may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. If reimbursement of our product is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed.

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.

Under the Creating and Restoring Equal Access to Equivalent Samples Act of 2019, or 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 REMS 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 fully comply 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 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, our flexible workplace policy which allows employees to work from home may make it difficult for us to maintain our corporate culture.

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 our Board of Directors;
- 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 of the 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. 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.

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

- our success in launching and commercializing PYRUKYND®;

- 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;
- 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 or pandemics, and any recession, depression or sustained market event resulting from such epidemics or pandemics;
- 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, 2024, 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 and 383 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, 2024, and determined that we

did not have a qualified ownership change since our last review as of December 31, 2023. 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 Coronavirus Aid, Relief, and Economic Security 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.

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 1C. Cybersecurity

We have certain processes for assessing, identifying and managing cybersecurity risks, which are built into our overall information technology function and are designed to help protect our information assets and operations from internal and external cyber threats, and protect employee, collaborator and patient information from unauthorized access or attack, as well as secure our networks and systems. Such processes include physical, procedural and technical safeguards, response plans, regular tests on our systems, incident simulations and routine review of our policies and procedures to identify risks and refine our practices. We engage certain external parties, including consultants, computer security firms and risk management advisors, peer companies, industry groups and governance experts, to enhance our cybersecurity oversight including by gaining valuable insights into the ever-evolving cybersecurity landscape. We consider the internal risk oversight programs of third-party service providers before engaging them in order to help protect us from any related vulnerabilities.

We do not believe that there are currently any known risks from cybersecurity threats that are reasonably likely to materially affect us or our business strategy, results of operations or financial condition.

The Audit Committee of our Board of Directors provides direct oversight over cybersecurity risk, and provides updates to the Board of Directors regarding such oversight. The Audit Committee receives periodic updates from management regarding cybersecurity matters, and is notified between such updates regarding significant new cybersecurity threats or incidents.

Our Vice President, Information Technology and Facilities, or the VP of IT, leads the operational oversight of company-wide cybersecurity strategy, policy, standards and processes and works across relevant departments to assess and help prepare us and our employees to address cybersecurity risks. Our VP of IT has worked in the information technology field for over 20 years at both biotechnology companies and management consulting firms, and holds a Bachelor of Science in Management and a Masters of Business Administration. We also maintain a team of experienced senior level engineers who design, implement and operate our information technology ecosystem, helping to implement cybersecurity best practices throughout our information technology infrastructure and governance processes. We periodically assess our processes against cybersecurity frameworks, such as the National Institute of Standards and Technology, or NIST, Cybersecurity Framework, Center for Internet Security, or CIS, Controls, and International Organization for Standardization, or ISO, 27001.

In an effort to deter and detect cyber threats, we annually provide all employees, including part-time and temporary employees, with a data protection, cybersecurity and incident response and prevention training and compliance program, which covers timely and relevant topics, including social engineering, phishing, password protection, confidential data protection, asset use and mobile security, and educates employees on the importance of reporting all incidents immediately. We also use technology-based tools that are designed to mitigate cybersecurity risks and to bolster our employee-based cybersecurity programs.

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 the 13,000 square feet at 38 Sidney Street, Cambridge, Massachusetts, which expired on December 31, 2024. In April 2022, we entered into a long-term sublease agreement for 27,000 square feet of office space at 64 Sidney Street, Cambridge, Massachusetts, with the term of the lease running through April 2025. In May 2023, we entered into a long-term sublease agreement for 7,407 square feet of office space on the first floor of 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.

Item 3. Legal Proceedings

As of December 31, 2024, 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 7, 2025, there were nine 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.

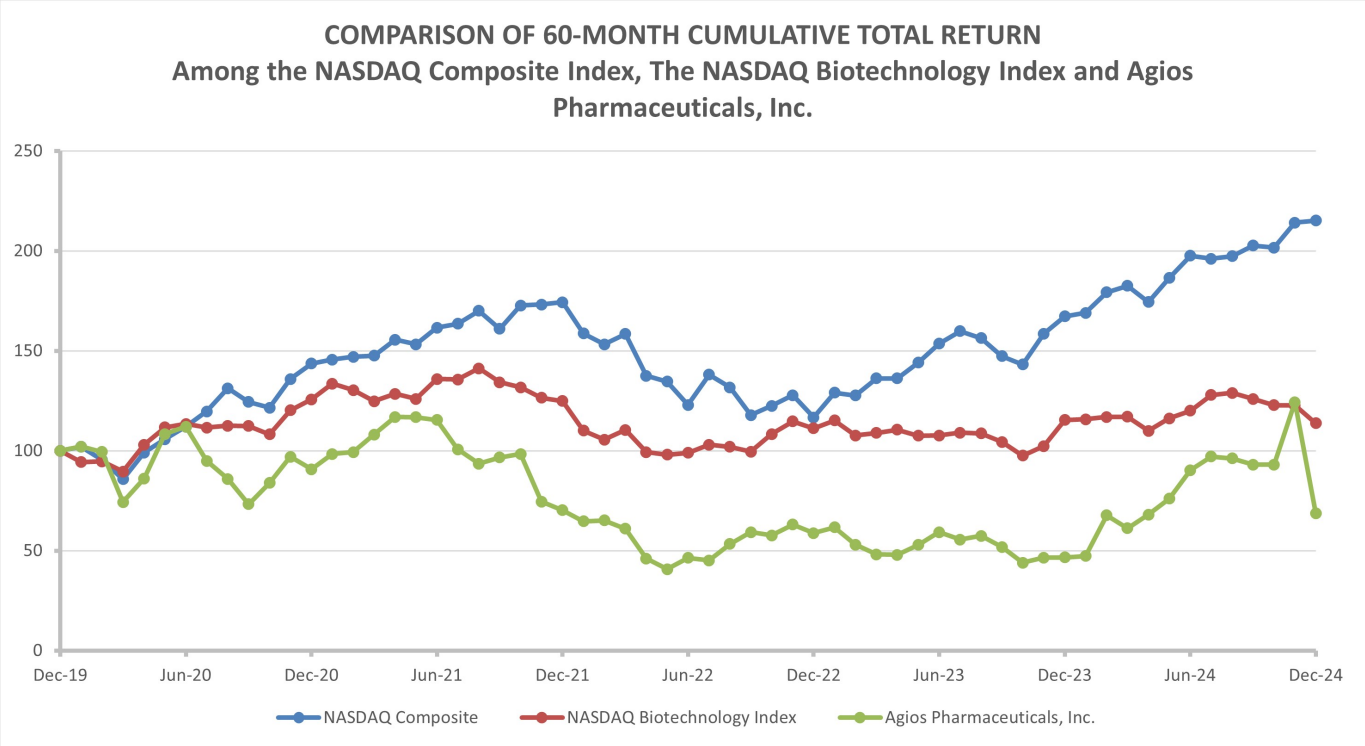
Securities Authorized for Issuance under Equity Compensation Plans

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, 2019 through December 31, 2024. The comparison assumes $100 was invested after the market closed on December 31, 2019 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

None.

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 medicines for rare diseases, with a focus on classical hematology. 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. 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. 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. PYRUKYND® is approved for use by the U.S. Food and Drug Administration, or FDA, for the treatment of hemolytic anemia in adults with PK deficiency in the United States and by the European Commission for the treatment of PK deficiency in adult patients in the European Union, or EU. Additionally, 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 December 2024, we announced that we submitted a supplemental new drug application, or sNDA, to the FDA for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia, which was accepted with standard review by the FDA and granted a Prescription Drug User Fee Act, or PDUFA, goal date of September 7, 2025. Also in December 2024, we announced that we submitted a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia.

In addition, we are currently evaluating PYRUKYND® in Phase 3 clinical trials for the treatment of sickle cell disease, or SCD, and in pediatric patients with PK deficiency. We are also developing (i) tebapivat, a novel PK activator, for the potential treatment of lower-risk myelodysplastic syndromes, or LR MDS, and hemolytic anemias; (ii) AG-181, our phenylalanine hydroxylase, or PAH, stabilizer for the potential treatment of phenylketonuria, or PKU; and (iii) AG-236, an siRNA in-licensed from Alnylam Pharmaceuticals, Inc., or Alnylam, targeting the transmembrane serine protease 6, or TMPRSS6 gene for the potential treatment of polycythemia vera, or PV.

Alnylam License Agreement

In accordance with the license agreement with Alnylam, in the year ended December 31, 2023, we made an up-front payment to Alnylam and recognized in-process research and development of $17.5 million which was recorded in research and development expense within our consolidated statements of operations and classified as investing activities within our consolidated statements of cash flows. We will also pay Alnylam for certain expenses associated with the development of AG-236, an siRNA targeting the TMPRSS6 gene, and these will be recorded in our consolidated statements of operations as incurred. Additionally, we are responsible to pay up to $130.0 million in potential development and regulatory milestones, in addition to sales milestones as well as tiered royalties on annual net sales, if any, of licensed products, which may be subject to specified reductions and offsets. Because the acquired assets under the license agreement with Alnylam do not meet the definition of a business in accordance with Accounting Standards Codification, or ASC, 805, *Business Combinations*, we accounted for the agreement as an asset acquisition.

Sale of Oncology Business to Servier Pharmaceuticals, LLC (Servier) and Sale of Contingent Payments

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, or IDH, 1 or 2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), or the Vorasidenib Milestone Payment, 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, or the Vorasidenib Royalty Rights. The Vorasidenib Milestone Payment, Vorasidenib Royalty Rights and royalty payments related to TIBSOVO® are referred to as contingent payments and recognized as income when realizable. 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 agreed to conduct certain clinical development activities within the IDHIFA® development program.

In October 2022, we sold our rights to future contingent payments associated with the royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through the loss of exclusivity 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.

In August 2024, the FDA approved vorasidenib for adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, following surgery including biopsy, sub-total resection, or gross total resection. In September 2024, we received the Vorasidenib Milestone Payment from Servier and recognized income of $200.0 million within the milestone payment from gain on sale of oncology business line item in our consolidated statements of operations for the year ended December 31, 2024. In May 2024, we entered into a purchase and sale agreement to sell the Vorasidenib Royalty Rights to Royalty Pharma Investments 2019 ICAV, or Royalty Pharma, for $905.0 million in cash, or the Upfront Payment. The sale was contingent upon FDA approval of vorasidenib and other customary closing conditions.

Upon consummation of the sale in August 2024, Royalty Pharma acquired 100% of the Vorasidenib Royalty Rights payments made by Servier on account of up to $1.0 billion in U.S. net sales for each calendar year. In addition, any such Vorasidenib Royalty Rights payments made by Servier on account of U.S. net sales in each calendar year in excess of $1.0 billion will be split, with Royalty Pharma having the rights to a 12% earn-out on those excess payments and Agios retaining the rights to a 3% earn-out on those excess payments, or the Retained Earn-Out Rights. As a result of the sale, we recognized income of $889.1 million ($905.0 million net of fees of $15.9 million) within the gain on sale of contingent payments line item in our consolidated statements of operations for the year ended December 31, 2024. Royalty income related to the Retained Earn-Out Rights, if any, will be recognized in the period when realizable.

Financial Operations Overview

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 and classical hematology, 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 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, potential royalty payments with respect to the Retained Earn-Out Rights, the actual and potential future sales of PYRUKYND® and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, we may pursue opportunistic debt offerings, and equity or equity-linked offerings.

Additionally, since inception, we have historically incurred significant operating losses. Our net income for the year ended December 31, 2024 was $673.7 million, our net loss for the year ended December 31, 2023 was $352.1 million and our net loss for the year ended December 31, 2022 was $231.8 million. As of December 31, 2024, we had an accumulated deficit of $148.9 million. The net income we generated in the year ended December 31, 2024 was primarily due to the sale of the Vorasidenib Royalty Rights to Royalty Pharma and our receipt of the Vorasidenib Milestone Payment discussed above in *Overview*. We expect to continue 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 and commercialization activities for PYRUKYND®, including with respect to the review by the FDA and other regulatory authorities of our regulatory submissions made, which we announced in December 2024, for the treatment of thalassemia; continue to advance and expand clinical development of tebapivat, our novel PK activator; continue to advance clinical development of AG-181, our PAH stabilizer; continue preclinical development of AG-236, a licensed siRNA development candidate pursuant to our license agreement with Alnylam; 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 PYRUKYND® 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®. In July 2024, we entered into a distribution agreement, or the NewBridge Agreement, with NewBridge Pharmaceuticals FZ-LLC, or NewBridge, pursuant to which we granted NewBridge the right to commercialize PYRUKYND® in Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and the United Arab Emirates, or the GCC region. 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 Annual Report on Form 10-K.

In the future, we expect to continue to generate revenue from product sales. We may also generate revenue from milestone payments, upfront payments or royalties on product sales under collaborations or licensing agreements that we may enter into in the future.

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 years ended December 31, 2024, December 31, 2023 and December 31, 2022 were expensed prior to February 17, 2022, and, therefore, are not included in costs of sales during the years ended December 31, 2024, December 31, 2023 and December 31, 2022. The amounts excluded from cost of sales were not significant during the years ended December 31, 2024, December 31, 2023 and December 31, 2022.

Inventories are reviewed periodically to identify excess or obsolete inventory based on projected sales activity as well as product shelf-life. Expired inventory is disposed of, and the related costs are recognized as cost of sales in our consolidated statements of operations, when, based on the expiry date, we do not believe we are able to sell the inventory. We have not reserved for excess or obsolete inventory during the years ended December 31, 2024 and December 31, 2023.

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 portfolio to increase 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 development of 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;
- successfully enrolling in, and completion of, clinical trials;
- receiving 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, in the United States or in other jurisdictions, whether alone or in collaboration with others, including pursuant to the NewBridge Agreement; and
- maintaining an acceptable safety profile of the products following approval.

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

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

- employee-related expenses, including salaries, benefits and stock-based compensation expense;
- expenses incurred under agreements with third parties, including contract research organizations, or CROs, that conduct research and development and both preclinical and clinical activities on our behalf, and the cost of consultants;
- the cost of lab supplies and acquiring, developing and manufacturing preclinical study and clinical trial 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.

PYRUKYND® is approved for use by the FDA for the treatment of hemolytic anemia in adults with PK deficiency in the United States and by the European Commission for the treatment of PK deficiency in adult patients in the EU. Additionally, 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 December 2024, we announced that we submitted an sNDA to the FDA for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia, which was accepted with standard review by the FDA and granted a PDUFA goal date of September 7, 2025. Also in December 2024, we announced that we submitted an MAA to the EMA and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia. In addition, we are currently evaluating PYRUKYND® in clinical trials for the treatment of SCD and in pediatric patients with PK deficiency.

We have worldwide development and commercial rights to PYRUKYND®. In July 2024, we entered into a distribution agreement with NewBridge Pharmaceuticals FZ-LLC, or the NewBridge Agreement, pursuant to which we granted NewBridge the right to commercialize PYRUKYND® in the GCC region. We expect to fund the future development and commercialization costs related to this program. PYRUKYND® has been granted orphan drug designation for the treatment of PK deficiency by the FDA and the EMA. Additionally, PYRUKYND® has received orphan drug designation from the FDA for the treatment of thalassemia and SCD, orphan medicinal product designation from the EMA for the treatment of SCD, and breakthrough medicine designation from the Saudi Food and Drug Authority for the treatment of thalassemia.

We built our commercial infrastructure to support the commercialization of PYRUKYND® in adult PK deficiency in the United States, and have expanded this infrastructure to support the potential commercial launch of PYRUKYND® in thalassemia in the United States. In connection with our regulatory approvals in the EU and Great Britain, we are currently providing access to PYRUKYND® on a free of charge basis for eligible patients in those jurisdictions through a global managed access program. We provide access to PYRUKYND® for adult patients with PK deficiency in other jurisdictions upon request through the global managed access program, on either a free of charge or for charge basis. Our global managed access program has not had a significant impact on our business, financial condition or results of operations. 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, such as the NewBridge Agreement.

We are evaluating PYRUKYND® in numerous clinical trials, including the following:

- An extension study evaluating the long-term safety, tolerability and efficacy of treatment with PYRUKYND® in patients from ENERGIZE, our completed phase 3, double-blind, randomized, placebo-controlled multicenter study pivotal trial of PYRUKYND® in adults with non-transfusion-dependent alpha- or beta-thalassemia. We announced topline data for ENERGIZE in January 2024 and a more detailed analysis of the data in June 2024. A total of 194 patients were enrolled in the study, with 130 randomized to PYRUKYND® 100 mg twice-daily, or BID, and 64 randomized to matched placebo. 122 patients (93.8%) in the PYRUKYND® arm and 62 patients (96.9%) in the placebo arm completed the 24-week double-blind period of the study. The study met the primary endpoint of hemoglobin response, where treatment with PYRUKYND® demonstrated a statistically significant increase in hemoglobin response compared to placebo, as 42.3% of patients in the PYRUKYND® arm achieved a hemoglobin response, compared to 1.6% of patients in the placebo arm (2-sided $p<0.0001$). Treatment with PYRUKYND® also demonstrated statistically significant improvements compared to placebo for both key secondary endpoints: (i) change from baseline in average Functional Assessment of Chronic Illness Therapy-Fatigue, or FACIT-Fatigue, subscale score from week 12 to week 24 and (ii)

change from baseline in average hemoglobin concentration from week 12 to week 24. During the 24-week double-blind period, four (3.1%) subjects in the PYRUKYND® arm experienced adverse events, or AEs, leading to discontinuation, and there were no AEs in the placebo arm leading to discontinuation. AEs that led to discontinuation in the PYRUKIND® arm were thrombocytopenia, arthralgia, abdominal distension, and 5 concurrent laboratory adverse events (alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increase, blood LDH increase, and international normalized ratio increase), all in one patient each.

- An extension study evaluating the long-term safety, tolerability and efficacy of treatment with PYRUKYND® in patients from ENERGIZE-T, our completed 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 alpha- or beta-thalassemia, defined as 6 to 20 red blood cell, or RBC, units transfused and ≤ six-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. We announced topline data for ENERGIZE-T in June 2024 and a more detailed analysis of the data in December 2024. A total of 258 patients were enrolled in the study, with 171 randomized to PYRUKYND® 100 mg twice-daily and 87 randomized to matched placebo. 155 patients (90.6%) in the PYRUKYND® arm and 83 patients (95.4%) in the placebo arm completed the 48-week double-blind period of the study. The study met the primary endpoint of transfusion reduction response, where treatment with PYRUKYND® demonstrated a statistically significant reduction in transfusion burden compared to placebo, as 30.4% of patients achieved a transfusion reduction response, compared to 12.6% of patients in the placebo arm (2-sided p=0.0003). Treatment with PYRUKYND® also demonstrated a statistically significant reduction in additional measures of transfusion reduction response compared to placebo as assessed by the three key secondary endpoints: (i) ≥50% reduction in transfused RBC units in any consecutive 24-week period through week 48 compared with baseline, (ii) ≥33% reduction in transfused RBC units from week 13 through week 48 compared with baseline, and (iii) ≥50% reduction in transfused RBC units from week 13 through week 48 compared with baseline. In addition, a higher proportion of patients in the PYRUKYND® arm (9.9%) compared to the placebo arm (1.1%) achieved the secondary endpoint of transfusion independence (transfusion-free for ≥8 consecutive weeks through week 48). The proportion of patients with any treatment-emergent adverse events, or TEAEs, was 90.1% in patients on PYRUKYND® and 83.5% in patients on placebo. The most frequent TEAEs that occurred in at least 10% of patients on PYRUKYND® were headache, upper respiratory tract infection, initial insomnia, diarrhea and fatigue. Serious TEAEs were reported in 11.0% and 15.3% of patients on PYRUKYND® and placebo, respectively; 2.3% and 1.2%, respectively, were considered treatment-related. During the 48-week double-blind period, 5.8% of the patients in the PYRUKYND® arm experienced a TEAE leading to discontinuation compared to 1.2% of patients in the placebo arm. The TEAEs leading to discontinuation of PYRUKYND®, each of which occurred in one patient, were diarrhea, paresthesia oral, concurrent anxiety and insomnia, initial insomnia, supraventricular tachycardia, fatigue, hypertransaminasemia, hepatitis C, hepatic cancer, and renal mass. The TEAE that led to discontinuation of the one patient on placebo was blood creatine phosphokinase increase.

  As indicated above, during the double-blind periods of ENERGIZE and ENERGIZE-T, two patients on PYRUKYND® experienced events of hepatocellular injury. In addition, during the open-label extension periods of both trials, a total of three patients experienced events of hepatocellular injury after switching from placebo to PYRUKYND®. All of these events occurred within the first six months of exposure to PYRUKYND® and liver tests improved following discontinuation of PYRUKYND®.

  Based on the results of the ENERGIZE and ENERGIZE-T trials, in December 2024 we announced that we filed regulatory applications for PYRUKYND® for the treatment of adult patients with non-transfusion-dependent and transfusion-dependent alpha- or beta-thalassemia with the FDA, EMA and Kingdom of Saudi Arabia and United Arab Emirates health authorities and we included in our regulatory applications hepatocellular injury as an important potential risk of PYRUKYND® in patients with thalassemia and proposed monthly monitoring of liver tests for the first six months of treatment with PYRUKYND®. We updated our PYRUKYND® clinical trial protocols across all indications to incorporate monthly monitoring of liver tests for the first six months of treatment and updated the U.S. Prescribing Information, or USPI, for PYRUKYND® for the treatment of hemolytic anemia in adults with PK deficiency to reflect the aforementioned hepatocellular injury and monitoring.
- 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, or SCPCs, in the past 12 months, and have hemoglobin within the range of 5.5 to 10.5 g/dL during screening. We enrolled 79 patients in the phase 2 portion of the trial, with 26 patients in the 50 mg twice daily mitapivat arm, 26 patients in the 100 mg twice daily mitapivat arm and 27 patients in the placebo arm. The primary endpoints of the phase 2 portion of the trial were hemoglobin response, defined as ≥ 1 g/dL increase in average hemoglobin concentration from week 10 to week 12 compared to baseline, and safety. In June 2023,

we announced the phase 2 portion of this trial had achieved its primary endpoint of hemoglobin response in patients in both the 50 mg and 100 mg twice daily mitapivat arms. 46.2% of patients (n=12) in the 50 mg twice daily mitapivat arm and 50.0% of patients (n=13) in the 100 mg twice daily mitapivat arm achieved a hemoglobin response, compared to 3.7% of patients (n=1) in the placebo arm (2-sided p=0.0003 and 0.0001, respectively). In December 2023, we announced the following additional results of the phase 2 portion of the trial: (i) the least-squares mean (95% confidence interval) for average change from baseline in hemoglobin levels, from week 10 through week 12, for patients in the 50 mg twice daily mitapivat, 100 mg twice daily mitapivat, and placebo arms, respectively, was 1.11 (0.77, 1.45) g/dL, 1.13 (0.79, 1.47) g/dL, and 0.05 (−0.28, 0.39) g/dL; (ii) we observed improvements in annualized rates of SCPCs as the annualized rate of SCPCs (95% confidence interval) for patients in the 50 mg twice daily and 100 mg twice daily mitapivat arms, respectively, was 0.83 (0.34, 1.99) and 0.51 (0.16, 1.59), compared to 1.71 (0.95, 3.08) for patients in the placebo arm; (iii) we observed improvement in patient-reported fatigue scores in the 50 mg twice daily mitapivat arm compared to the placebo arm, and the least-squares mean (95% confidence interval) for average changes from baseline in patient-reported fatigue score, from week 10 through week 12, for patients in the 50 mg twice daily mitapivat, 100 mg twice daily mitapivat, and placebo arms, respectively, was −3.80 (−7.16, −0.45), −0.10 (−3.27, 3.08), and −0.17 (−3.40, 3.07). The safety profile for mitapivat observed in the phase 2 portion of the trial was generally consistent with previously reported data in other studies of SCD and other hemolytic anemias. The most common TEAEs in the 50 mg BID, 100 mg BID, and placebo arms, respectively, were: headache (n=6, 6, 7), arthralgia (n=3, 5, 9), dysmenorrhea (n=0, 3, 0), pain (n=3, 3, 2), pain in extremity (n=1, 3, 6), back pain (n=4, 2, 3), nausea (n=1, 2, 4), fatigue (n=4, 1, 5), and influenza-like illness (n=1, 1, 3). There were no serious TEAEs attributed to mitapivat and there were no AEs leading to drug reduction, discontinuation, interruption or death in either the mitapivat or the placebo arms. Of the 79 patients enrolled in the study, 73 continued into the Phase 2 open-label extension period. In October 2023, we enrolled the first patient in the phase 3 portion of this trial and we have since enrolled over 200 patients worldwide. 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 (100 mg twice daily) PYRUKYND® dose level or the placebo. The primary endpoints are hemoglobin response, defined as ≥1 g/dL increase in average hemoglobin from week 24 through week 52 compared to baseline, and annualized rate of SCPCs. The secondary endpoints include additional clinical efficacy measures related to anemia, hemolysis, erythropoiesis, patient-reported fatigue and pain, annualized frequency of hospitalizations for SCPCs, and change from baseline in six minute walk test. 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®. We have completed enrollment and expect to announce topline data for this trial in late 2025, with a potential U.S. commercial launch in 2026, if approved.

- 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.

  A total of 49 patients were enrolled in ACTIVATE-kidsT, with 32 randomized to mitapivat twice-daily and 17 randomized to matched placebo. 30 patients (93.8%) in the mitapivat arm and 16 (94.1%) in the placebo arm completed the 32-week double-blind period of the study. 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. We announced topline data for ACTIVATE-kidsT in August 2024. Using Bayesian methodology, the prespecified statistical criterion for the primary endpoint in ACTIVATE-kidsT was not met using low or moderate borrowing of data from the ACTIVATE-T study in adults. In the study, 28.1% of patients in the mitapivat arm achieved the primary endpoint of transfusion reduction response, compared to 11.8% of patients in the placebo arm. Transfusion-free response and normal hemoglobin response were secondary endpoints in this study and only observed in patients in the mitapivat arm. In the 32-week double-blind treatment period, mitapivat was generally safe and well-tolerated, with safety results consistent with the safety profile for mitapivat previously observed in adults with PK deficiency who are regularly transfused.

  A total of 30 patients were enrolled in ACTIVATE-kids, with 19 randomized to mitapivat twice-daily and 11 randomized to matched placebo. All patients in both treatment arms completed the 20-week double-blind period of the study. 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. We announced topline data for ACTIVATE-kids in February 2025. Using Bayesian methodology, the prespecified statistical criterion for the primary endpoint in ACTIVATE-kids was met using a range of relative borrowing from the adult ACTIVATE study, for all possible borrowing weights (ranging from 0 to 1). In addition, the pre-specified supportive analysis based on traditional methodology comparing the hemoglobin response rate for mitapivat versus placebo provided further evidence that the primary endpoint was met. There were 31.6% of patients in the mitapivat arm achieving a hemoglobin response compared to 0% of patients in the placebo arm; the 95% confidence interval for the difference in hemoglobin response rates between mitapivat and placebo was >0 (95% CI=10.8% to 52.7%). In addition, improvements in changes from baseline for markers of hemolysis (indirect bilirubin,

lactate dehydrogenase and haptoglobin) were observed in the mitapivat arm compared to the placebo arm. In the 20-week double-blind period of the study, a similar proportion of patients had AEs in the mitapivat and placebo arms and there were no discontinuations of study treatment due to AEs or for any reason. The safety results from the trial were consistent with the safety profile for mitapivat previously observed for adult patients with PK deficiency who are not regularly transfused.

- 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.

Tebapivat: Novel PK Activator

We are developing tebapivat, a novel PK activator for the potential treatment of LR MDS and hemolytic anemias. Tebapivat has been granted orphan drug designation for the treatment of MDS by the FDA.

We have completed a phase 1 clinical trial evaluating tebapivat in healthy volunteers and patients with SCD, and we expect to dose the first patient in a phase 2 clinical trial of tebapivat in adult patients with SCD in mid-2025.

We also initiated a phase 2a clinical trial of tebapivat in adults with LR MDS in the third quarter of 2022, and the trial has completed enrollment with 22 patients, including 12 patients classified as non-transfused and 10 patients classified as low transfusion burden. Patients received 5 mg of tebapivat once daily for up to 16 weeks. The two primary endpoints of the trial were transfusion independence (for patients classified as low transfusion burden), defined as transfusion-free for ≥ eight consecutive weeks during the 16-week treatment period, and hemoglobin response, defined as a ≥ 1.5 g/dL increase from baseline in the average hemoglobin concentration measured from week 8 through week 16.

In November 2023, we announced that we achieved clinical proof-of-concept in the phase 2a portion of the trial. We observed that four of the 10 patients with low transfusion burden achieved the transfusion independence endpoint, and one of the 22 patients achieved the hemoglobin response endpoint in the 16-week treatment period. The safety profile observed was consistent with data reported in the healthy volunteer study of tebapivat. 19 patients elected to enroll in the extension period for up to 156 weeks. We evaluated the phase 2a trial results and assessed the impact of those results on the phase 2b portion of the protocol, and based on the data generated in the phase 2a portion of the trial, we plan to increase the dosage levels evaluated in the phase 2b portion of the trial, which we initiated in the third quarter of 2024. We expect to complete enrollment in this phase 2b trial in late 2025.

Other Programs

In addition to the aforementioned development programs, we are developing AG-181, a PAH stabilizer for the potential treatment of PKU, for which we filed an IND in December 2023. We initiated a phase 1 clinical trial of AG-181 in healthy volunteers in the first quarter of 2024. Also, in July 2023, we entered into a license agreement with Alnylam for the development and commercialization of products containing or comprised of an siRNA preclinical development candidate discovered by Alnylam and targeting the TMPRSS6 gene, and we have begun preclinical development of a product candidate, AG-236, for the potential treatment of patients with PV. We expect to file an investigational new drug application, or IND, with the FDA for AG-236 for the treatment of PV in mid-2025.

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 portfolio, including the ongoing commercialization of PYRUKYND® and any of our other product candidates, which may include the hiring of additional personnel.

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 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 ASC 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 PYRUKYND® 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 trials and preclinical development activities; (ii) investigative sites in connection with clinical trials; 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*, 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.

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 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 performance-based vesting conditions, we recognize stock-based compensation expense if the performance condition is considered probable of achievement using management's best estimates.

Results of Operations

Comparison of years ended December 31, 2024, 2023 and 2022

Revenues

(In thousands)	2024	2023	2022
Revenues:			
Product revenue, net	$ 36,498	$ 26,823	$ 11,740
Milestone revenue	—	—	2,500
Total revenue	$ 36,498	$ 26,823	$ 14,240

Total Revenue – 2024 vs. 2023 – The increase in total revenue of $9.7 million in 2024 compared to 2023 was due to increased volume associated with PYRUKYND®.

Total Revenue – 2023 vs. 2022 – The increase in total revenue of $12.6 million in 2023 compared to 2022 was due to increased product revenue associated with PYRUKYND®, which was approved by the FDA in February 2022, partially offset by revenue recognized in 2022 associated with the licensing of intellectual property for our Friedreich's Ataxia preclinical program.

Total Operating Expenses

(In thousands)	2024	2023	2022
Operating expenses			
Cost of sales	$ 4,165	$ 2,881	$ 1,704
Research and development	301,286	295,526	279,910
Selling, general and administrative	156,784	119,903	121,673
Total Operating Expenses	$ 462,235	$ 418,310	$ 403,287

Total Operating Expenses – 2024 vs. 2023 – The increase in total operating expenses of $43.9 million in 2024 compared to 2023 was primarily due to an increase of $36.9 million in selling, general and administrative expenses, driven by an increase in commercial-related activities as we prepare for the potential approval of PYRUKYND® in thalassemia, and an increase of $5.8 million in research and development expenses, which is described below under Research and Development Expenses.

Total Operating Expenses – 2023 vs 2022 – The increase in total operating expenses of $15.0 million in 2023 compared to 2022 was primarily due to an increase of $15.6 million in research and development expenses, which is described below under Research and Development Expenses.

Research and Development Expenses

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

(In thousands)	2024	2023	2022
PK activator (PYRUKYND®)	$ 112,720	$ 101,322	$ 83,271
Novel PK activator (tebapivat)	14,544	18,267	15,747
In-process research and development	—	17,500	—
Other research and platform programs	20,730	11,492	26,837
Total direct research and development expenses	147,994	148,581	125,855
Compensation and related expenses	114,618	108,484	109,248
Facilities and IT related expenses & other	38,674	38,461	43,290
Other expenses - transition services	—	—	1,517
Total indirect research and development expenses	153,292	146,945	154,055
Total research and development expense	$ 301,286	$ 295,526	$ 279,910

Total Research and Development Expenses – 2024 vs. 2023 – The increase in research and development expenses of $5.8 million in 2024 compared to 2023 was due to a $6.3 million increase in our indirect expenses, partially offset by a $0.6 million decrease in our direct expenses. The increase in indirect expenses was primarily due to a $6.1 million increase in compensation and related expenses due to an increase in workforce related expenses. The decrease in direct expenses was due to the $17.5 million up-front payment in 2023 associated with the Alnylam license agreement discussed above under Overview

and a decrease of $3.7 million in tebapivat costs due to decreased costs associated with clinical trials of tebapivat in patients with SCD and MDS, offset by an $11.4 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 increased process development expenses and increased costs associated with clinical trials for patients with SCD, partially offset by lower costs associated with the phase 3 clinical trials of PYRUKYND® in patients with thalassemia, ENERGIZE and ENERGIZE-T. The increase in other research and platform programs was primarily a result of costs associated with AG-236, the in-licensed siRNA TMPRSS6 program for PV.

Total Research and Development Expenses – 2023 vs 2022 – The increase in research and development expenses of $15.6 million in 2023 compared to 2022 was due to a $22.7 million increase in our direct expense offset by a $7.1 million decrease in our indirect expenses. The increase in direct expenses was primarily due to a $18.1 million increase in PYRUKYND® costs and in-process research and development from the $17.5 million up-front payment associated with the license agreement with Alnylam discussed above under Overview, offset by a $15.3 million decrease 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, and increased process development and medical affairs expenses. The decrease in other research and platform programs was primarily due to our decision to evolve our approach to exploratory research and drug discovery to focus on our existing late-lead optimization programs. The decrease in indirect expenses was primarily due to a $4.8 million decrease in facilities and IT related expenses & other due to a reduction in facility expenses associated with the evolution of our research organization, and the $1.5 million of reimbursable transition related services we provided to Servier in 2022 related to the sale of the oncology business for discovery, clinical development, technical operations, and related activities, which were completed during the three months ended March 31, 2022.

Other Income and Expense

(In thousands)	2024	2023	2022
Gain on sale of contingent payments	$ 889,136	$ —	$ 127,853
Milestone payment from gain on sale of oncology business	200,000	—	—
Royalty income from gain on sale of oncology business	—	—	9,851
Interest income, net	48,083	33,344	12,793
Other income, net	6,487	6,055	6,749

Other Income and Expense – 2024 vs. 2023 – The increase in gain on sale of contingent payments in 2024 compared to 2023 was due to the sale of the Vorasidenib Royalty Rights in 2024 discussed above in *Overview*. The increase in milestone payment from gain on sale of oncology business was due to the receipt of the Vorasidenib Milestone Payment in 2024 as discussed above in *Overview*. The $14.7 million increase in interest income, net in 2024 compared to 2023 is primarily attributable to increased return on our investments.

Other Income and Expense – 2023 vs 2022 – The decrease in gain on sale of contingent payments and royalty income from gain on sale of oncology business in 2023 compared to 2022 was due to the sale to Sagard in the fourth quarter of 2022 of our rights to future contingent payments associated with royalties on U.S. next sales of TIBSOVO®. The $20.6 million increase in interest income, net in 2023 compared to 2022 is primarily attributable to an increase in interest rates. The $0.7 million decrease in other income, net in 2023 compared to 2022 primarily related to approximately $2.6 million of reimbursable transition related services and fees for the sale of the oncology business in 2022, partially offset by sublease income of $6.1 million in 2023 compared to $4.1 million in 2022.

Net Income (Loss)

(In thousands)	2024	2023	2022
Net income (loss) before taxes	$ 717,969	$ (352,088)	$ (231,801)
Income tax expense	44,244	—	—
Net income (loss)	673,725	(352,088)	(231,801)

Net Income (Loss) – 2024 vs 2023 – The increase in net income in 2024 compared to 2023 was primarily driven by the sale of the Vorasidenib Royalty Rights in 2024 discussed above in *Overview* and the receipt of the Vorasidenib Milestone Payment in 2024 discussed above in *Overview*, partially offset by the increase in income tax expense as a result of the income related to the sale of the Vorasidenib Royalty Rights and the receipt of the Vorasidenib Milestone Payment.

Net Income (Loss) – 2023 vs 2022 – The $120.3 million increase in net loss in 2023 compared to 2022 was primarily driven by the gain on sale of contingent payments in 2022 described above in Other Income and Expense, higher research and development expenses discussed above under Research and Development Expenses, which includes the $17.5 million up-front

payment associated with the license agreement with Alnylam discussed above under Overview, and the decrease in royalty income from gain on sale of oncology business described above in Other Income and Expense. These were partially offset by the increase in interest income, net discussed above in Other Income and Expense and the increase in revenue discussed above under Revenues.

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, potential royalty payments with respect to the Retained Earn-Out Rights, the actual and potential future sales of PYRUKYND® and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, we may pursue opportunistic debt offerings, and equity or equity-linked offerings.

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 the right to the Vorasidenib Milestone Payment, 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 the Vorasidenib Royalty Rights. The Vorasidenib Milestone Payment, Vorasidenib Royalty Rights and royalty payments related to TIBSOVO® are referred to as contingent payments and recognized as income when realizable. Servier also acquired our co-commercialization rights for Bristol Myers Squibb's IDHIFA® and the right to receive a $25.0 million potential milestone payment under our prior collaboration agreement with Celgene, and following the sale Servier has agreed to conduct certain clinical development activities within the IDHIFA® development program. As discussed in Note 1, *Nature of Business* to the consolidated financial statements in this Annual Report on Form 10-K, in October 2022, we sold our rights to the royalty on U.S. net sales of TIBSOVO® to Sagard for $131.8 million, but we retained our rights to the Vorasidenib Milestone Payment and Vorasidenib Royalty Rights.

In August 2024, the FDA approved vorasidenib for adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, following surgery including biopsy, sub-total resection, or gross total resection. In September 2024, we received the Vorasidenib Milestone Payment from Servier and recognized income of $200.0 million within the milestone payment from gain on sale of oncology business line item in our consolidated statements of operations for the year ended December 31, 2024. In May 2024, we entered into a purchase and sale agreement to sell the Vorasidenib Royalty Rights to Royalty Pharma Investments 2019 ICAV, or Royalty Pharma, for $905.0 million in cash, or the Upfront Payment. The sale was contingent upon FDA approval of vorasidenib and other customary closing conditions.

Upon consummation of the sale in August 2024, Royalty Pharma acquired 100% of the Vorasidenib Royalty Rights payments made by Servier on account of up to $1.0 billion in U.S. net sales for each calendar year. In addition, any such Vorasidenib Royalty Rights payments made by Servier on account of U.S. net sales in each calendar year in excess of $1.0 billion will be split, with Royalty Pharma having the rights to a 12% earn-out on those excess payments and Agios retaining the rights to a 3% earn-out on those excess payments, or the Retained Earn-Out Rights. As a result of the sale, we recognized income of $889.1 million ($905.0 million net of fees of $15.9 million) within the gain on sale of contingent payments line item in our consolidated statements of operations for the year ended December 31, 2024. Royalty income related to the Retained Earn-Out Rights, if any, will be recognized in the period when realizable.

Our cash, cash equivalents and marketable securities balance was $1.5 billion at December 31, 2024. The Retained Earn-Out Rights discussed above are our only committed potential external sources of funds. We cannot predict what success, if any, Servier may have in the United States with respect to the sale of vorasidenib, and consequently, we cannot estimate the amount of payments, if any, we may receive on account of the Retained Earn-Out Rights.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2024, 2023 and 2022:

(In thousands)	2024	2023	2022
Net cash used in operating activities	$ (389,841)	$ (296,062)	$ (309,478)
Net cash provided by investing activities	363,441	239,575	243,261
Net cash provided by financing activities	14,442	5,433	2,350
Net change in cash and cash equivalents	$ (11,958)	$ (51,054)	$ (63,867)

Net cash used in operating activities

Cash used in operating activities of $389.8 million during the year ended December 31, 2024 was primarily due to operating expenses driven by research and development costs described above under Research and Development Expenses, partially offset by cash received related to interest income of $43.5 million and cash received from product revenues of $37.8 million.

Cash used in operating activities of $296.1 million during the year ended December 31, 2023 was primarily due to operating expenses driven by research and development costs described above under Research and Development Expenses, partially offset by cash received related to interest income of $31.2 million and cash received from revenues of $28.6 million.

Cash used in operating activities of $309.5 million during the year ended December 31, 2022 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.

Net cash provided by investing activities

Cash provided by investing activities of $363.4 million during the year ended December 31, 2024 was primarily due to the proceeds from the Upfront Payment from Royalty Pharma and the Vorasidenib Milestone Payment from Servier, partially offset by higher purchases of marketable securities than proceeds from maturities and sales of marketable securities as a result of the proceeds from the Upfront Payment and the Vorasidenib Milestone Payment.

The cash provided by investing activities for the year ended December 31, 2023 was primarily due to higher proceeds from maturities and sales of marketable securities than purchases of marketable securities, partially offset by the $17.5 million up-front payment associated with the Alnylam license agreement discussed above under Overview.

The cash provided by investing activities for the year ended December 31, 2022 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.

Net cash provided by financing activities

The cash provided by financing activities for the year ended December 31, 2024 was due to $14.4 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, 2023 was due to $5.4 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, 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.

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 portfolio, including as we continue to commercialize PYRUKYND®. If we obtain additional marketing approvals for PYRUKYND® in thalassemia or in other indications, or 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, 2024, together with anticipated product revenue and interest income, will provide the financial independence to prepare for potential PYRUKYND® commercial launches in thalassemia and SCD, advance our existing programs, and opportunistically expand our pipeline through both internally and externally discovered assets. Our expectations regarding our long-term funding requirements are

based on assumptions that may prove to be wrong, and we may need additional capital resources to fund our operating plans and capital expenditure requirements.

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 payments, if any, we may receive on account of the Retained Earn-Out Rights;
- the costs and timing of our ongoing and future commercialization activities, including product manufacturing, sales, marketing and distribution for PYRUKYND® in the approved jurisdictions and for any product candidate for which we may receive approval;
- 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, including the amount and timing of future milestone and royalty payments potentially payable to Alnylam pursuant to the license agreement;
- the costs, timing and outcome of regulatory review of our product candidates, including with respect to regulatory submissions for PYRUKYND® for the treatment of thalassemia;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- 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 public health epidemics; and
- operational delays, disruptions and/or increased costs associated with global economic and political developments, 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, potential royalty payments with respect to the Retained Earn-Out Rights, the actual and potential future sales of PYRUKYND® and, potentially, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. In addition, 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 Retained Earn-Out Rights. 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, selling or licensing our assets, 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, 2024:

	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)	$ 62,328	$ 17,943	$ 40,906	$ 3,479	$ —
Manufacturing arrangements (2)	942	314	628	—	—
Service arrangements (3)	6,625	3,142	1,742	1,741	—

(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. Arrangement is for a contractual term of five years, however, the total funds can be allocated in any manner to meet the agreement terms.

We also 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.

In July 2023, we entered into a license agreement with Alnylam as discussed above under Overview and under Note 1, *Nature of Business*, to our consolidated financial statements. Under the license agreement, we may be required to pay up to $130.0 million in potential development and regulatory milestones, in addition to sales milestones as well as tiered royalties on annual net sales, if any, of licensed products, which may be subject to specified reductions and offsets. Such payment obligations are contingent upon the occurrence of future events and the timing and likelihood of such potential obligations are not known.

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, 2024 and December 31, 2023, we had cash, cash equivalents and marketable securities of $1.5 billion and $0.8 billion, respectively, consisting primarily of investments in U.S. Treasuries, government securities, corporate debt securities and certificates of deposit. 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 and 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, 2024 and December 31, 2023, 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, 2024, our principal executive officer and

principal financial officer concluded that our disclosure controls and procedures as of such date are effective at the reasonable assurance level. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act 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, 2024. 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, 2024, 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, 2024, 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, 2024 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

(b) Director and Officer Trading Arrangements

A significant portion of the compensation of our directors and officers (as defined in Rule 16a-1(f) under the Exchange Act) is in the form of equity awards and, from time to time, directors and officers engage in open-market transactions with respect to the securities acquired pursuant to such equity awards or other of our securities, including to satisfy tax withholding obligations when equity awards vest or are exercised, and for diversification or other personal reasons.

Transactions in our securities by directors and officers are required to be made in accordance with our insider trading policy, which requires that the transactions be in accordance with applicable U.S. federal securities laws that prohibit trading while in possession of material nonpublic information. Rule 10b5-1 under the Exchange Act provides an affirmative defense that enables directors and officers to prearrange transactions in our securities in a manner that avoids concerns about initiating transactions while in possession of material nonpublic information.

Each Rule 10b5-1 trading arrangement described below was entered into in accordance with our insider trading policy, and only permitted or permits transactions upon the expiration of the applicable mandatory cooling-off periods under Rule 10b5-1 of the Exchange Act. Actual transactions are required to be disclosed publicly in Section 16 filings with the SEC.

The following table describes, for the fourth quarter of 2024, each trading arrangement for the sale or purchase of Company securities adopted or terminated by our directors and officers that is either (1) a contract, instruction or written plan intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) (a "Rule 10b5-1 trading arrangement") or (2) a "non-Rule 10b5-1 trading arrangement" (as defined in Item 408(c) of Regulation S-K):

Name (Title)	Action Taken (Date of Action)	Type of Trading Arrangement	Nature of Trading Arrangement	Duration of Trading Arrangement	Aggregate Number of Securities
Cecilia Jones (Chief Financial Officer)	Adoption (December 13, 2024)	Rule 10b5-1 trading arrangement	Sale	Through and including March 17, 2026	Up to 24,779 shares
Tsveta Milanova (Chief Commercial Officer)	Adoption (December 13, 2024)	Rule 10b5-1 trading arrangement	Sale	Through and including March 17, 2026	Up to 18,831 shares

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 2025 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 2025 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 2025 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 2025 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 2025 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-28 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	10-K	001-36014	February 23, 2023	2.2	
3.1	Restated Certificate of Incorporation of the Registrant	8-K	001-36014	July 30, 2013	3.1	
3.2	Third Amended and Restated By-Laws	8-K	001-36014	March 3, 2023	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#	2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.4	
10.2#	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.5	
10.3#	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.6	
10.4#	Amended and Restated 2013 Employee Stock Purchase Plan					X

10.5	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-189216	July 11, 2013	10.12
10.6	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
10.7	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
10.8#	Summary Description of Annual Cash Incentive Program	10-Q	001-36014	May 11, 2015	10.1
10.9	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
10.10#	Form of Performance Share Unit Agreement under 2013 Stock Incentive Plan	10-K	001-36014	February 26, 2016	10.25
10.11	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
10.12	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
10.13	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
10.14#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for employees)	10-Q	001-36014	May 4, 2018	10.1
10.15#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for directors)	10-K	001-36014	February 14, 2019	10.32
10.16	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
10.17	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
10.18	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
10.19	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
10.20	Sublease Agreement, dated April 14, 2023, between the Registrant and Watershed Informatics, Inc.	10-K	001-36014	February 15, 2024	10.21
10.21#	Letter Agreement, dated July 8, 2022, between the Registrant and Brian Goff	10-Q	001-36014	August 4, 2022	10.2
10.22#	Form of Inducement Stock Option Agreement for Brian Goff	10-Q	001-36014	August 4, 2022	10.3
10.23#	Form of Inducement Restricted Stock Unit Agreement for Brian Goff	10-Q	001-36014	August 4, 2022	10.4

10.24#**	Form of Inducement Performance Stock Unit Agreement for Brian Goff	10-Q	001-36014	August 4, 2022	10.5	
10.25#	Letter Agreement, dated as of September 16, 2022, between the Registrant and Cecilia Jones	10-Q	001-36014	November 3, 2022	10.5	
10.26#	Form of Inducement Stock Option Agreement for Cecilia Jones	S-8	333-267624	September 26, 2022	99.1	
10.27#	Form of Inducement Restricted Stock Unit Agreement for Cecilia Jones	S-8	333-267624	September 26, 2022	99.2	
10.28#**	Form of Inducement Performance Stock Unit Agreement for Cecilia Jones	S-8	333-267624	September 26, 2022	99.3	
10.29#	Amended and Restated Severance Benefits Plan	8-K	001-36014	October 7, 2022	10.1	
10.30#	Letter Agreement, dated as of December 5, 2022, between the Registrant and Tsveta Milanova	10-K	001-36014	February 23, 2023	10.38	
10.31#	Form of Inducement Stock Option Agreement for Tsveta Milanova	S-8	333-269018	January 3, 2023	99.1	
10.32#	Form of Inducement Restricted Stock Unit Agreement for Tsveta Milanova	S-8	333-269108	January 3, 2023	99.2	
10.33#**	Form of Inducement Performance Stock Unit Agreement for Tsveta Milanova	S-8	333-269108	January 3, 2023	99.3	
10.34#	2023 Stock Incentive Plan	S-8	333-272615	June 13, 2023	99.1	
10.35#	Form of Stock Option Agreement Under 2023 Stock Incentive Plan	10-Q	001-36014	August 3, 2023	10.2	
10.36#	Form of Restricted Stock Unit Agreement Under 2023 Stock Incentive Plan	10-Q	001-36014	August 3, 2023	10.3	
10.37#	Form of Restricted Stock Unit Agreement (Performance-Based) Under 2023 Stock Incentive Plan	10-Q	001-36014	August 3, 2023	10.4	
10.38**	Purchase and Sale Agreement, dated May 24, 2024, by and between the Registrant and Royalty Pharma Investments 2019 ICAV	10-Q	001-36014	August 1, 2024	10.1	
19.1	Insider Trading Policy					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
97.1	Dodd-Frank Compensation Recovery Policy	10-K	001-36014	February 15, 2024	97.1	
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 13, 2025

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 13, 2025
/s/ Cecilia Jones Cecilia Jones	Chief Financial Officer (Principal financial officer)	February 13, 2025
/s/ T.J. Washburn T.J. Washburn	Vice President, Controller (Principal accounting officer)	February 13, 2025
/s/ Jacqualyn A. Fouse Jacqualyn A. Fouse, Ph.D.	Chair of the Board of Directors	February 13, 2025
/s/ Rahul Ballal Rahul Ballal, Ph.D.	Director	February 13, 2025
/s/ Jeffrey Capello Jeffrey Capello	Director	February 13, 2025
/s/ Kaye Foster Kaye Foster	Director	February 13, 2025
/s/ Maykin Ho Maykin Ho, Ph.D.	Director	February 13, 2025
/s/ Catherine Owen Catherine Owen	Director	February 13, 2025
/s/ David Scadden David Scadden, M.D.	Director	February 13, 2025
/s/ David P. Schenkein David P. Schenkein, M.D.	Director	February 13, 2025
/s/ Cynthia Smith Cynthia Smith	Director	February 13, 2025

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, 2024 and 2023, and the related consolidated statements of operations, of comprehensive (loss) income, of stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2024, 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, 2024, 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, 2024 and 2023**,** and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2024 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, 2024, 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.

Revenue Recognition - PYRUKYND® Product Revenue

As described in Notes 2 and 8 to the consolidated financial statements, the Company generates 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. 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 the Customers, healthcare providers, payors and other indirect customers relating to the sale of its products. For the year ended December 31, 2024, the Company recognized $36.5 million of net product revenue relating to the sale of PYRUKYND®.

The principal consideration for our determination that performing procedures relating to PYRUKYND® product revenue recognition is a critical audit matter is a high degree of auditor effort in performing procedures related to the Company's product revenue recognition.

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 relating to the revenue recognition process, including controls over the recording of PYRUKYND® product revenue at the transaction price once control passes to the customer. These procedures also included, among others, (i) evaluating management's revenue recognition policy and (ii) testing the completeness, accuracy, and occurrence of revenue recognized for a sample of product revenue transactions by obtaining and inspecting source documents, such as purchase orders, invoices, proof of delivery, and subsequent cash receipts.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
February 13, 2025

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:	2024	2023
Assets		
Current assets:		
Cash and cash equivalents	$ 76,247	$ 88,205
Marketable securities	817,463	688,723
Accounts receivable, net	4,109	2,810
Inventory	27,616	19,076
Prepaid expenses and other current assets	40,165	35,021
Total current assets	965,600	833,835
Marketable securities	638,321	29,435
Operating lease assets	42,879	54,409
Property and equipment, net	11,675	15,382
Other non-current assets	4,724	4,057
Total assets	$ 1,663,199	$ 937,118
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 16,643	$ 9,780
Accrued expenses	46,861	43,167
Income taxes payable	871	—
Operating lease liabilities	16,781	15,008
Total current liabilities	81,156	67,955
Operating lease liabilities, net of current portion	40,207	56,988
Other non-current liabilities	880	1,156
Total liabilities	122,243	126,099
Commitments and contingent liabilities (Note 14)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 25,000,000 shares authorized, no shares issued and outstanding at December 31, 2024 and 2023	—	—
Common stock, $0.001 par value; 125,000,000 shares authorized; 73,372,696 shares issued and 57,156,285 outstanding at December 31, 2024 and 72,161,489 shares issued and 55,945,078 outstanding at December 31, 2023	73	72
Additional paid-in capital	2,493,811	2,436,523
Accumulated other comprehensive loss	(1,518)	(441)
Accumulated deficit	(148,924)	(822,649)
Treasury stock, at cost (16,216,411 shares at December 31, 2024 and December 31, 2023)	(802,486)	(802,486)
Total stockholders' equity	1,540,956	811,019
Total liabilities and stockholders' equity	$ 1,663,199	$ 937,118

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:	2024	2023	2022
Revenues:			
Product revenue, net	$ 36,498	$ 26,823	$ 11,740
Milestone revenue	—	—	2,500
Total revenue	36,498	26,823	14,240
Operating expenses			
Cost of sales	$ 4,165	$ 2,881	$ 1,704
Research and development	301,286	295,526	279,910
Selling, general and administrative	156,784	119,903	121,673
Total operating expenses	462,235	418,310	403,287
Loss from operations	(425,737)	(391,487)	(389,047)
Gain on sale of contingent payments	889,136	—	127,853
Milestone payment from gain on sale of oncology business	200,000	—	—
Royalty income from gain on sale of oncology business	—	—	9,851
Interest income, net	48,083	33,344	12,793
Other income, net	6,487	6,055	6,749
Net income (loss) before taxes	717,969	(352,088)	(231,801)
Income tax expense	44,244	—	—
Net income (loss)	$ 673,725	$ (352,088)	$ (231,801)
Net income (loss) per share - basic	$ 11.86	$ (6.33)	$ (4.23)
Net income (loss) per share - diluted	$ 11.64	$ (6.33)	$ (4.23)
Weighted-average number of common shares used in computing net income (loss) per share – basic	56,807,415	55,651,487	54,789,435
Weighted-average number of common shares used in computing net income (loss) per share – diluted	57,889,255	55,651,487	54,789,435

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Comprehensive Income (Loss)

(In thousands) Years Ended December 31:	2024	2023	2022
Net income (loss)	$ 673,725	$ (352,088)	$ (231,801)
Other comprehensive (loss) income			
Unrealized (loss) gain on available-for-sale securities	(1,077)	12,094	(11,337)
Comprehensive income (loss)	$ 672,648	$ (339,994)	$ (243,138)

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Stockholders' Equity

(In thousands, except share amounts)	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Treasury		Total Stockholders' Equity
	Shares	Amount				Shares	Amount	
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
Common stock issued under stock incentive plan and ESPP	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
Unrealized gain on available-for-sale securities	—	—	—	12,094	—	—	—	12,094
Net loss	—	—	—	—	(352,088)	—	—	(352,088)
Stock-based compensation expense	—	—	44,766	—	—	—	—	44,766
Common stock issued under stock incentive plan and ESPP	905,371	1	5,432	—	—	—	—	5,433
Balance at December 31, 2023	72,161,489	$ 72	$ 2,436,523	$ (441)	$ (822,649)	(16,216,411)	$ (802,486)	$ 811,019
Unrealized loss on available-for-sale securities	—	—	—	(1,077)	—	—	—	(1,077)
Net income	—	—	—	—	673,725	—	—	673,725
Stock-based compensation expense	—	—	42,847	—	—	—	—	42,847
Common stock issued under stock incentive plan and ESPP	1,211,207	1	14,441	—	—	—	—	14,442
Balance at December 31, 2024	73,372,696	$ 73	$ 2,493,811	$ (1,518)	$ (148,924)	(16,216,411)	$ (802,486)	$ 1,540,956

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows

(In thousands) Years Ended December 31:	2024	2023	2022
Operating activities			
Net income (loss)	$ 673,725	$ (352,088)	$ (231,801)
Adjustments to reconcile net income (loss) to net cash used in operating activities:			
Depreciation and amortization	5,653	6,623	8,564
Stock-based compensation expense	42,847	44,766	49,296
Net accretion of discount on marketable securities	(14,486)	(5,051)	(1,198)
Gain on sale of contingent payments	(889,136)	—	(127,853)
Loss (gain) on disposal of property and equipment	(39)	553	(48)
Non-cash operating lease expense	11,530	10,720	9,995
Expense associated with license agreement	—	17,500	—
Realized gain on investments	(167)	(28)	—
Milestone payment from gain on sale of oncology business	(200,000)	—	—
Changes in operating assets and liabilities:			
Accounts receivable, net	(1,299)	(604)	(2,206)
Inventory	(8,540)	(10,584)	(8,492)
Other receivables	—	—	447
Prepaid expenses and other current and non-current assets	(5,811)	3,833	(176)
Accounts payable	6,601	(8,733)	3,436
Accrued expenses	3,694	12,817	(1,617)
Income taxes payable	871	—	—
Operating lease liabilities	(15,008)	(13,663)	(10,828)
Other liabilities	(276)	(2,123)	3,003
Net cash used in operating activities	(389,841)	(296,062)	(309,478)
Investing activities			
Purchases of marketable securities	(1,542,433)	(417,930)	(1,030,781)
Proceeds from maturities and sales of marketable securities	818,383	674,679	1,146,175
Proceeds from sale of contingent payments	889,136	—	131,784
Proceeds from milestone payment from gain on sale of oncology business	200,000	—	—
Payments associated with license agreement	—	(17,500)	—
Purchases of property and equipment	(1,685)	(999)	(4,881)
Proceeds from sale of equipment	40	1,325	964
Net cash provided by investing activities	363,441	239,575	243,261
Financing activities			
Payments on financing lease obligations	—	—	(331)
Net proceeds from stock option exercises and employee stock purchase plan	14,442	5,433	2,681
Net cash provided by financing activities	14,442	5,433	2,350
Net change in cash and cash equivalents	(11,958)	(51,054)	(63,867)
Cash and cash equivalents at beginning of the period	88,205	139,259	203,126
Cash and cash equivalents at end of the period	$ 76,247	$ 88,205	$ 139,259
Supplemental disclosure of non-cash investing and financing transactions:			
Additions to property and equipment in accounts payable and accrued expenses	$ 317	$ 55	$ 158
Net cash taxes paid	$ 43,150	$ 1,569	$ —

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," "Agios," "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 medicines for rare diseases, with a focus on classical hematology. 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. 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. 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. PYRUKYND® is approved for use by the U.S. Food and Drug Administration, or FDA, for the treatment of hemolytic anemia in adults with PK deficiency in the United States and by the European Commission for the treatment of PK deficiency in adult patients in the European Union, or EU. Additionally, 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 December 2024, we announced that we submitted a supplemental new drug application, or sNDA, to the FDA for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia, which was accepted with standard review by the FDA and granted a Prescription Drug User Fee Act, or PDUFA, goal date of September 7, 2025. Also in December 2024, we announced that we submitted a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, and regulatory applications to the Kingdom of Saudi Arabia and United Arab Emirates health authorities for PYRUKYND® for the treatment of adult patients with non-transfusion dependent and transfusion-dependent alpha- or beta-thalassemia.

In addition, we are currently evaluating PYRUKYND® in Phase 3 clinical trials for the treatment of sickle cell disease, or SCD, and in pediatric patients with PK deficiency. We are also developing (i) tebapivat, a novel PK activator, for the potential treatment of lower-risk myelodysplastic syndromes, or LR MDS, and hemolytic anemias; (ii) AG-181, our phenylalanine hydroxylase, or PAH, stabilizer for the potential treatment of phenylketonuria, or PKU; and (iii) AG-236, an siRNA in-licensed from Alnylam Pharmaceuticals, Inc., or Alnylam, targeting the transmembrane serine protease 6, or TMPRSS6 gene for the potential treatment of polycythemia vera, or PV.

We are subject to risks common to companies in our industry including, but not limited to, uncertainties relating to conducting preclinical and 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, potential product liability claims and potential government investigations.

Alnylam License Agreement

On July 28, 2023, we entered into a license agreement with Alnylam under which we acquired the rights to develop and commercialize Alnylam's novel preclinical siRNA targeting the TMPRSS6 gene, as a potential disease-modifying treatment for patients with PV. Because the acquired assets do not meet the definition of a business in accordance with Accounting Standards Codification, or ASC, 805, *Business Combinations*, we accounted for the agreement as an asset acquisition.

In accordance with the license agreement, in the year ended December 31, 2023, we made an up-front payment to Alnylam and recognized in-process research and development of $17.5 million which was recorded in research and development expense within our consolidated statements of operations and classified as investing activities within our consolidated statements of cash flows. We will also pay Alnylam for certain expenses associated with the development of AG-236, an siRNA targeting the TMPRSS6 gene, and these will be recorded in our consolidated statements of operations as incurred. Additionally, we are responsible to pay up to $130.0 million in potential development and regulatory milestones, in addition to sales milestones as

well as tiered royalties on annual net sales, if any, of licensed products, which may be subject to specified reductions and offsets.

Sale of Oncology Business to Servier and Sale of Contingent Payments

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 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, or IDH, 1 or 2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), or the Vorasidenib Milestone Payment, 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, or the Vorasidenib Royalty Rights. The Vorasidenib Milestone Payment, Vorasidenib Royalty Rights and royalty payments related to TIBSOVO® are referred to as contingent payments and recognized as income when realizable. 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 has agreed to conduct certain clinical development activities within the IDHIFA® development program.

In October 2022, we sold our rights to future contingent payments associated with the royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through the loss of exclusivity 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, 2023.

In August 2024, the FDA approved vorasidenib for adult and pediatric patients 12 years and older with Grade 2 astrocytoma or oligodendroglioma with a susceptible IDH1 or IDH2 mutation, following surgery including biopsy, sub-total resection, or gross total resection. In September 2024, we received the Vorasidenib Milestone Payment from Servier and recognized income of $200.0 million within the milestone payment from gain on sale of oncology business line item in our consolidated statements of operations for the year ended December 31, 2024. In May 2024, we entered into a purchase and sale agreement to sell the Vorasidenib Royalty Rights to Royalty Pharma Investments 2019 ICAV, or Royalty Pharma, for $905.0 million in cash, or the Upfront Payment. The sale was contingent upon FDA approval of vorasidenib and other customary closing conditions.

Upon consummation of the sale in August 2024, Royalty Pharma acquired 100% of the Vorasidenib Royalty Rights payments made by Servier on account of up to $1.0 billion in U.S. net sales for each calendar year. In addition, any such Vorasidenib Royalty Rights payments made by Servier on account of U.S. net sales in each calendar year in excess of $1.0 billion will be split, with Royalty Pharma having the rights to a 12% earn-out on those excess payments and Agios retaining the rights to a 3% earn-out on those excess payments, or the Retained Earn-Out Rights. As a result of the sale, we recognized income of $889.1 million ($905.0 million net of fees of $15.9 million) within the gain on sale of contingent payments line item in our consolidated statements of operations for the year ended December 31, 2024. Royalty income related to the Retained Earn-Out Rights, if any, will be recognized in the period when realizable.

We recorded income from royalties of $9.9 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.

Liquidity

As of December 31, 2024, we had cash, cash equivalents and marketable securities of $1.5 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.

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 ASC 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 PYRUKYND® 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 years ended December 31, 2024, 2023 and 2022 were expensed prior to February 17, 2022 and, therefore, are not included in costs of sales during the years ended December 31, 2024, 2023 and 2022. The amounts excluded from cost of sales were not significant during the years ended December 31, 2024, 2023 and 2022.

Inventories are reviewed periodically to identify excess or obsolete inventory based on projected sales activity as well as product shelf-life. Expired inventory is disposed of, and the related costs are recognized as cost of sales in our consolidated statements of operations, when, based on the expiry date, we do not believe we are able to sell the inventory. We have not reserved for excess or obsolete inventory during the years ended December 31, 2024 and 2023.

Marketable securities

Marketable securities at December 31, 2024 and 2023 consisted of investments in U.S. Treasuries, government securities, corporate debt securities and certificates of deposit. 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 income (loss) in the consolidated statements of comprehensive income (loss), until realized. Realized gains and losses are included in interest income, net on a specific-identification basis.

At December 31, 2024 and 2023, we held both current and non-current investments. Investments classified as current are those that: (i) have a maturity of less than one year, or (ii) have a maturity of one to two years but we intend to liquidate within the next twelve months. 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 one year, 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, 2024 or 2023. 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, 2024 and 2023. 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, 2024.

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, 2024.

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 trials, 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 as of a given balance sheet date 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 performance-based vesting conditions, we recognize stock-based compensation expense 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 income (loss) and unrealized gains and losses on available-for-sale securities. Accumulated other comprehensive loss consists entirely of unrealized gains and losses from available-for-sale securities as of December 31, 2024 and 2023.

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 the weighted-average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury stock method. For purposes of the dilutive net income (loss) per share calculation, stock options, restricted stock units, or RSUs, and performance-based stock units, or PSUs, for which the performance and market vesting conditions, respectively, have been deemed probable, and 2013 Employee Stock Purchase Plan, or 2013 ESPP, shares are considered to be common stock equivalents, while PSUs with performance and market vesting conditions, respectively, that were not deemed probable as of December 31, 2024 are not considered to be common stock equivalents.

We utilize the control number concept in the computation of diluted earnings per share to determine whether potential common stock equivalents are dilutive. The control number used is net income (loss) from continuing operations. The control number concept requires that the same number of potentially dilutive securities applied in computing diluted earnings per share from continuing operations be applied to all other categories of income or loss, regardless of their anti-dilutive effect on such categories. Since we had a net loss for the years ended December 31, 2023 and 2022, no dilutive effect was recognized in the calculation of loss per share and basic and diluted net loss per share was the same for those periods.

Segment 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 CODM, or decision-making group in making decisions on how to allocate resources and assess performance. Our CODM is our chief executive officer, or CEO. Our CEO views our operations and manages our business as one operating segment, which derives its revenues from the development and commercialization of therapies for patients with rare diseases.

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. 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 repurchases, retirements or re-issuances of treasury stock during the year ended December 31, 2024.

Recent accounting pronouncements

In December 2023, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, 2023-09, *Income Taxes (Topics 740): Improvements to Income Tax Disclosures*, to expand the disclosure requirements for income taxes. Upon adoption, companies will be required to disclose additional specified categories in the rate reconciliation. Companies will also be required to disclose the amount of income taxes paid disaggregated by jurisdiction, among other disclosure requirements. The standard is effective for annual periods beginning after December 15, 2024, and can be applied either prospectively or retrospectively. We plan to adopt the standard in our 2025 annual period and are currently assessing its effect on our financial statement disclosures.

In November 2024, the FASB issued ASU 2024-03, *Income Statement – Reporting Comprehensive Income – Expense Disaggregation Disclosures (Subtopic 220-40): Disaggregation of Income Statement Expenses*, to improve disclosures around an entity's expenses. Upon adoption, companies will be required to disclose in the notes to the financial statements a disaggregation of certain expense categories included within the expense captions on the face of the income statement. The

standard is effective for annual periods beginning after December 15, 2026 and interim periods beginning after December 15, 2027, with early adoption permitted, and can be applied either prospectively or retrospectively. We plan to adopt the standard in our 2027 annual period and are currently assessing its effect the standard on our financial statement disclosures.

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, 2024:

(In thousands)	Level 1	Level 2	Level 3	Total
Cash equivalents	$ 44,988	$ 3,386	$ —	$ 48,374
Total cash equivalents	44,988	3,386	—	48,374
Marketable securities:				
Certificates of deposit	—	10,385	—	10,385
U.S. Treasuries	—	281,119	—	281,119
Government securities	—	279,707	—	279,707
Corporate debt securities	—	884,573	—	884,573
Total marketable securities	—	1,455,784	—	1,455,784
Total cash equivalents and marketable securities	$ 44,988	$ 1,459,170	$ —	$ 1,504,158

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, 2024.

Note 4. Marketable Securities

Marketable securities at December 31, 2024 consisted of the following:

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
Certificates of deposit	$ 10,374	$ 11	$ —	$ 10,385
U.S. Treasuries	173,465	153	(27)	173,591
Government securities	167,970	103	(75)	167,998
Corporate debt securities	465,427	321	(259)	465,489
Total Current	817,236	588	(361)	817,463
Non-current:				
U.S. Treasuries	107,725	106	(303)	107,528
Government securities	112,175	3	(469)	111,709
Corporate debt securities	420,166	181	(1,263)	419,084
Total Non-current	640,066	290	(2,035)	638,321
Total marketable securities	$ 1,457,302	$ 878	$ (2,396)	$ 1,455,784

Marketable securities at December 31, 2023 consisted of the following:

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
U.S. Treasuries	$ 30,876	$ —	$ (56)	$ 30,820
Government securities	247,460	194	(695)	246,959
Corporate debt securities	411,045	874	(975)	410,944
Total Current	689,381	1,068	(1,726)	688,723
Non-current:				
U.S. Treasuries	4,802	30	—	4,832
Government securities	9,986	75	—	10,061
Corporate debt securities	14,430	112	—	14,542
Total Non-current	29,218	217	—	29,435
Total marketable securities	$ 718,599	$ 1,285	$ (1,726)	$ 718,158

There were no material realized gains or losses on marketable securities for the years ended December 31, 2024 and 2023.

At December 31, 2024 and 2023, we held 213 and 151 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, 2024 and 2023 related to these securities. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2024 and 2023 was $768.1 million and $513.5 million, respectively. There were no individual securities that were in a significant unrealized loss position as of December 31, 2024 and 2023. 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, 2024 and 2023.

Note 5. Inventory

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

(In thousands)	December 31, 2024	December 31, 2023
Raw materials	$ 89	$ 51
Work-in-process	24,509	17,568
Finished goods	3,018	1,457
Total inventory	$ 27,616	$ 19,076

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 three 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.

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.

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

(In thousands)	2024	2023	2022
Operating lease costs	$ 15,227	$ 15,227	$ 15,227
Cash paid for amounts included in the measurement of operating lease liabilities	18,705	18,170	17,035

We have not entered into any material short-term leases or financing leases as of December 31, 2024.

In arriving at the operating lease liabilities as of December 31, 2024, we applied the weighted-average incremental borrowing rate of 5.7% from inception over a weighted-average remaining lease term of 3.2 years. In arriving at the operating lease liabilities as of December 31, 2023, we applied the weighted-average incremental borrowing rate of 5.7% over a weighted-average remaining lease term of 4.2 years.

As of December 31, 2024, undiscounted minimum rental commitments under non-cancelable leases, for each of the next five years and total thereafter, were as follows:

(In thousands)	
2025	$ 17,943
2026	20,151
2027	20,755
2028	3,479
Undiscounted minimum rental commitments	62,328
Interest	(5,340)
Total operating lease liabilities	$ 56,988

We provided our landlord a security deposit of $2.9 million as security for our leases, which is included within other non-current assets on our consolidated balance sheet.

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, which expired on December 31, 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. At the end of the initial sublease period, the subtenant has the option to extend the lease for one additional 6-month period.

In May 2023, we entered into a long-term sublease agreement for 7,407 square feet of office space on the first floor of 64 Sidney Street, Cambridge, Massachusetts, with the term of the lease running through April 2025. At the end of the initial sublease period, the subtenant has the option to extend the lease for one additional year, followed by a second extension option for twenty-two additional months.

We recorded operating sublease income of $6.4 million and $6.1 million for the years ended December 31, 2024 and December 31, 2023, respectively, in other income, net in the consolidated statements of operations. We hold security deposits from our sublessees of approximately $0.9 million which is recorded within other non-current assets on our consolidated balance sheet.

As of December 31, 2024, the future minimum lease payments to be received under the long-term sublease agreements were as follows:

(In thousands)	
2025	$ 1,310
Total	$ 1,310

Note 7. Accrued Expenses

Accrued expenses consisted of the following at December 31:

(In thousands)	2024	2023
Accrued compensation	$ 29,935	$ 23,232
Accrued research and development costs	10,548	15,463
Accrued professional fees	4,316	3,115
Accrued other	2,062	1,357
Total accrued expenses	$ 46,861	$ 43,167

Note 8. 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 PYRUKYND® 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)	2024	2023	2022
Product revenue, net	$ 36,498	$ 26,823	$ 11,740

One Customer accounted for 95%, 96% and 97% of our consolidated revenues for the years ended December 31, 2024, 2023 and 2022, respectively, and 92% and 97% of accounts receivable from product sales for the years ended December 31, 2024 and 2023, respectively.

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 tables summarize balances and activity in each of the product revenue allowance and reserve categories for the years ended December 31, 2024 and December 31, 2023:

(In thousands)	Contractual Adjustments	Government Rebates	Returns	Total
Balance at December 31, 2023	$ 156	$ 1,084	$ 232	$ 1,472
Current provisions relating to sales in the current year	1,300	2,593	399	4,292
Adjustments relating to prior years	(39)	(711)	(45)	(795)
Payments/returns relating to sales in the current year	(1,079)	(1,239)	—	(2,318)
Payments/returns relating to sales in the prior years	(85)	(373)	(97)	(555)
Balance at December 31, 2024	$ 253	$ 1,354	$ 489	$ 2,096

(In thousands)	Contractual Adjustments	Government Rebates	Returns	Total
Balance at December 31, 2022	$ 65	$ 573	$ 133	$ 771
Current provisions relating to sales in the current year	1,079	2,086	2,182	5,347
Adjustments relating to prior years	—	(237)	(77)	(314)
Payments/returns relating to sales in the current year	(938)	(1,003)	(1,958)	(3,899)
Payments/returns relating to sales in the prior years	(50)	(335)	(48)	(433)
Balance at December 31, 2023	$ 156	$ 1,084	$ 232	$ 1,472

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

(In thousands)	December 31, 2024	December 31, 2023
Reduction of accounts receivable	$ 124	$ 151
Component of accrued expenses	1,972	1,321
Total revenue-related reserves	$ 2,096	$ 1,472

The following table presents changes in our contract assets, which consisted of accounts receivable, net:

(In thousands)	December 31, 2024	December 31, 2023
Beginning balance	$ 2,810	$ 2,206
Additions [1]	39,973	31,855
Deductions [1]	(38,674)	(31,251)
Ending balance	$ 4,109	$ 2,810

(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.

Note 9. Share-Based Payments

2023 Stock Incentive Plan and Inducement Grants

In June 2023, our stockholders approved the 2023 Stock Incentive Plan, or the 2023 Plan. The 2023 Plan provides for the grant of incentive stock options, nonstatutory stock options, stock appreciation rights, restricted stock awards, RSUs, PSUs, and other stock-based awards to employees, advisors, consultants and non-employee directors.

Following the adoption of the 2023 Plan, we ceased granting equity awards under the 2013 Stock Incentive Plan, or the 2013 Plan. Any outstanding equity awards that were previously granted under the 2013 Plan continue to be governed by their terms. Following adoption of the 2013 Plan, we ceased granting equity awards under the 2007 Stock Incentive Plan, or the 2007 Plan. There are no outstanding equity awards under the 2007 Plan.

In connection with the start of employment of our Chief Executive Officer and Chief Financial Officer in 2022, and our Chief Commercial Officer in 2023, our board of directors granted each of them equity awards in the form of stock options, RSUs and PSUs, which awards were made outside our equity incentive plans as inducements material to their respective entry into employment with us in accordance with Nasdaq Listing Rule 5635(c)(4).

As of December 31, 2024, the maximum number of shares reserved under the 2013 Plan, the 2023 Plan and the inducement grants described above was 10,896,149, and we had 2,868,747 shares available for future issuance under the 2023 Plan.

Stock options

The following table summarizes the stock option activity of all stock incentive plans for the year ended December 31, 2024:

	Number of Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2023	5,263,681	$ 44.94	6.36	$ 423
Granted	1,050,087	34.40		
Exercised	(343,341)	34.39		
Cancelled/Forfeited	(79,253)	39.00		
Expired	(56,918)	71.76		
Outstanding at December 31, 2024	5,834,256	$ 43.48	6.21	$ 11,911
Exercisable at December 31, 2024	3,851,037	$ 49.62	5.02	$ 6,574
Vested and expected to vest at December 31, 2024	5,834,256	$ 43.48	6.21	$ 11,911

The weighted-average grant date fair value of options granted was $18.92, $14.32 and $15.64 during the years ended December 31, 2024, 2023 and 2022, respectively. The total intrinsic value of options exercised was $3.3 million, $2.9 million and $0.3 million during the years ended December 31, 2024, 2023 and 2022, respectively.

At December 31, 2024, the total unrecognized compensation expense related to unvested stock option awards was $29.1 million, which we expect to recognize over a weighted-average period of approximately 2.37 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, 2024:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2023	1,346,701	$ 29.67
Granted	1,144,164	32.33
Vested	(594,511)	32.70
Forfeited	(77,791)	30.86
Unvested shares at December 31, 2024	1,818,563	$ 30.31

As of December 31, 2024, there was approximately $33.6 million of total unrecognized compensation expense related to RSUs, which we expect to be recognized over a weighted-average period of 1.87 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, 2024:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2023	362,133	$ 30.66
Granted	183,000	32.27
Vested	(170,550)	35.04
Unvested shares at December 31, 2024	374,583	$ 29.45

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, 2024, 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 was $11.0 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 market-based stock units, or 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, 2024:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2023	42,695	$ 41.50
Expired	(42,695)	41.50
Unvested shares at December 31, 2024	—	$ —

As of December 31, 2024, there was no remaining unrecognized compensation expense related to MSUs.

Amended and Restated 2013 Employee Stock Purchase Plan

In June 2013, our Board of Directors adopted, and in July 2013 our stockholders approved, the 2013 ESPP, which was further amended and restated by our Board of Directors in December 2024. We issued 102,805 shares and 112,832 shares during the years ended December 31, 2024 and 2023, respectively, under the 2013 ESPP. The 2013 ESPP provides participating employees with the opportunity to purchase up to an aggregate of 2,363,636 shares of our common stock. As of December 31, 2024, we had 1,583,234 shares available for future issuance under the 2013 ESPP.

Stock-based compensation expense

During the years ended December 31, 2024, 2023 and 2022, we recorded stock-based compensation expense for employee and non-employee stock options, RSUs, PSUs, and ESPP shares. Stock-based compensation expense by award type included within the consolidated statements of operations is as follows:

(In thousands)	2024	2023	2022
Stock options	$ 17,519	$ 17,163	$ 23,731
Restricted stock units	23,553	19,367	21,670
Performance-based stock units	750	7,368	2,919
Employee Stock Purchase Plan	1,025	868	976
Total stock-based compensation expense	$ 42,847	$ 44,766	$ 49,296

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

(In thousands)	2024	2023	2022
Research and development expense	$ 16,910	$ 17,064	$ 20,988
Selling, general and administrative expense	25,937	27,702	28,308
Total stock-based compensation expense	$ 42,847	$ 44,766	$ 49,296

No related tax benefits were recognized for the years ended December 31, 2024, 2023 and 2022.

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:

	2024	2023	2022
Risk-free interest rate	4.15 %	4.05 %	2.55 %
Expected dividend yield	—	—	—
Expected term (in years)	6.02	5.99	6.03
Expected volatility	53.32 %	54.26 %	55.30 %

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 the plain-vanilla nature of our share-based awards.

Volatility

The expected volatility has been determined using our 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 the weighted-average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury stock method. For purposes of the dilutive net income (loss) per share calculation, stock options, RSUs and PSUs 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 with performance and market vesting conditions, respectively, that were not deemed probable as of December 31, 2024 are not considered to be common stock equivalents.

We utilize the control number concept in the computation of diluted earnings per share to determine whether potential common stock equivalents are dilutive. The control number used is net income (loss) from continuing operations. The control number concept requires that the same number of potentially dilutive securities applied in computing diluted earnings per share from continuing operations be applied to all other categories of income or loss, regardless of their anti-dilutive effect on such categories. Since we had a net loss for the years ended December 31, 2023 and 2022, no dilutive effect was recognized in the calculation of loss per share and basic and diluted net loss per share was the same for those periods.

The following is a reconciliation of basic weighted-average number of common shares used in computing net income (loss) per share to diluted weighted-average number of common shares used in computing net income (loss) per share for the periods indicated:

	Years ended December 31,		
	2024	2023	2022
Basic shares	56,807,415	55,651,487	54,789,435
Effect of dilutive securities			
Stock options	336,446	—	—
Restricted stock units	732,925	—	—
Performance-based stock units	8,845	—	—
Employee stock purchase plan shares	3,624	—	—
Diluted shares	57,889,255	55,651,487	54,789,435

The following common stock equivalents were excluded from the calculation of diluted net income (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,		
	2024	2023	2022
Stock options	3,926,330	5,263,681	5,772,564
Restricted stock units	95,679	1,346,701	1,117,921
Performance-based stock units	—	145,023	—
Employee Stock Purchase Plan shares	3,987	48,713	42,026
Total	4,025,996	6,804,118	6,932,511

Note 11. Income Taxes

The domestic and foreign components of income (loss) before income taxes are as follows:

(In thousands)	2024	2023	2022
Domestic	$ 717,967	$ (352,085)	$ (231,767)
Foreign	2	(3)	(34)
Total	$ 717,969	$ (352,088)	$ (231,801)

We did not have any provision for income taxes for the years ended December 31, 2023 and 2022.

A reconciliation of the expected income tax expense (benefit) computed using the federal statutory income tax rate to our effective income tax rate is as follows for the years ended December 31, 2024, 2023 and 2022:

	2024	2023	2022
Federal statutory tax rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal benefit	1.6 %	1.9 %	2.9 %
Change in valuation allowance	(14.5)%	(23.8)%	(25.7)%
General business credits and other credits	(2.6)%	4.2 %	5.2 %
Permanent differences and other adjustments	0.6 %	(2.8)%	(2.3)%
Stock based compensation	0.1 %	(0.5)%	(1.1)%
Total	6.2 %	— %	— %

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, 2024 and 2023 are as follows:

(In thousands)	2024	2023
Deferred tax assets:		
Net operating loss carryforwards	$ 26,492	$ 64,066
Tax credit carryforwards	83,994	180,635
Purchased intangible assets	12,713	14,155
Stock-based compensation	21,090	20,954
Operating lease liability	13,023	16,780
Non-deductible accruals and reserves, including inventory	8,635	5,134
Section 174 R&D expense	121,530	93,333
Total deferred tax assets	287,477	395,057
Depreciation and amortization	(1,193)	(1,986)
Operating lease right of use asset	(10,713)	(13,411)
Less: valuation allowance	(275,571)	(379,660)
Net deferred taxes	$ —	$ —

The Tax Cuts and Jobs Act, or TCJA, requires taxpayers to capitalize and amortize research and experimental expenditures under Internal Revenue Code section 174 for tax years beginning after December 31, 2021. We capitalized research and experimental costs of $244.9 million and $232.7 million for the years ended December 31, 2024 and December 31, 2023, respectively. We will amortize these costs for tax purposes over 5 years if the research and experimentation was performed in the U.S. and over 15 years if the research and experimentation was performed outside the U.S.

As of December 31, 2024, we had net operating loss carryforwards, or NOLs, available to reduce state and foreign income taxes of approximately $320.0 million and $65.2 million, respectively. At December 31, 2024, we also had available research and development tax credits for federal and state income tax purposes of approximately $23.2 million and $29.3 million, respectively. If not utilized, the credits begin to expire in 2040 and 2028 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, 2024, we had available orphan drug tax credits for federal purposes only of approximately $37.5 million. If not utilized, the orphan drug credits begin to expire in 2040.

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, 2024 and determined that transactions have resulted in no ownership changes during the year ended December 31, 2024, 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 $275.6 million and $379.7 million as of December 31, 2024 and December 31, 2023, respectively, because we have determined that it is more likely than not that these assets will not be fully realized. The valuation allowance decreased by $104.1 million for the year ended December 31, 2024 and increased by $83.7 million for the year ended December 31, 2023. The decrease for the year ended December 31, 2024 relates primarily to the utilization of tax attributes to offset taxable income, and the increase for the year ended December 31, 2023 primarily due to the Section 174 R&D expense capitalization.

The following table presents our change in valuation allowance for the years ended December 31, 2024 and, 2023:

(In thousands)	2024	2023
Valuation allowance at the beginning of the year	$ 379,660	$ 295,993
Increase (decrease) for the current period	(104,089)	83,667
Valuation allowance at the end of the year	$ 275,571	$ 379,660

As of December 31, 2024, 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, 2024 and 2023:

(In thousands)	2024	2023
Unrecognized tax benefits at the beginning of the year	$ 28,578	$ 26,190
Gross increases - current period tax positions	3,013	2,388
Unrecognized tax benefits at the end of the year	$ 31,591	$ 28,578

We will recognize interest and penalties related to uncertain tax positions above the line as an expense to continuing operations. As of December 31, 2024 and 2023, we had no accrued interest or penalties related to uncertain tax positions and no such amounts have been recognized. If all of our unrecognized tax benefits as of December 31, 2024 were to become recognizable in the future, we would record $31.6 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, 2024, 2023, 2022, and 2021, although carryforward attributes that were generated for tax years prior to 2021 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 assessments in Switzerland, the Netherlands and Italy remains open for tax years ending December 31, 2024, 2023, 2022, 2021 and 2020. Our subsidiary in Germany has statute of limitations for assessments open are for the tax years ending December 31, 2024, 2023, 2022, and 2021, and our subsidiary in France has statute of limitations for assessments for the tax years ending December 31, 2024, 2023, and 2022. There are currently no federal, state or foreign audits in progress.

As of December 31, 2024 we had an income tax payable of $0.9 million and as of December 31, 2023 we had an income tax receivable of $1.1 million, which is recorded within prepaid expenses and other current assets in our consolidated balance sheets.

Note 12. Property and Equipment, net

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

(In thousands)	2024	2023
Laboratory equipment	$ 17,529	$ 17,433
Computer equipment and software	6,454	6,566
Leasehold improvements	37,519	37,277
Furniture and fixtures	3,454	3,459
Office equipment	2,319	2,268
Construction in progress	897	608
Total property and equipment	68,172	67,611
Less: accumulated depreciation	(56,497)	(52,229)
Total property and equipment, net	$ 11,675	$ 15,382

Depreciation expense for the years ended December 31, 2024, 2023 and 2022 was $5.7 million, $6.6 million and $8.4 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. 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 15. Defined Contribution Benefit Plan

We sponsor a 401(k) retirement plan, in which substantially all 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.

Note 16. Segment Information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the CODM or decision-making group in making decisions on how to allocate resources and assess performance. Our CODM is our CEO. Our CEO views our operations and manages our business as one operating segment, which derives its revenues from the development and commercialization of therapies for patients with rare diseases.

Our CEO manages and allocates resources to the operations of our company on a total company basis by assessing the overall level of resources available and how to best deploy these resources across functions and research and development projects that are in line with our long-term company-wide strategic goals. In making these decisions, our CEO uses consolidated financial information for purposes of evaluating performance, forecasting future period financial results, allocating resources and setting incentive targets. The CODM performs this assessment based on the Company's consolidated net income (loss). Through this analysis, the CODM assesses performance by comparing actual consolidated net income (loss) versus the budget, and then decides how to allocate resources to invest in the Company's research and development programs. The measure of segment assets is reported on the consolidated balance sheets as total assets.

The following table contains additional information on our consolidated revenue and net income (loss), including significant segment expenses:

(In thousands) Years Ended December 31:	2024	2023	2022
Product revenue, net	$ 36,498	$ 26,823	$ 11,740
PK activator (PYRUKYND®) direct expenses - research and development	(112,720)	(101,322)	(83,271)
Compensation and related expenses - research and development	(114,618)	(108,484)	(109,248)
Total selling, general and administrative expenses	(156,784)	(119,903)	(121,673)
Gain on sale of contingent payments	889,136	—	127,853
Milestone payment from gain on sale of oncology business	200,000	—	—
Other segment items*	(67,787)	(49,202)	(57,202)
Net income (loss)	$ 673,725	$ (352,088)	$ (231,801)

*Other segment items primarily include milestone revenue, cost of sales, other research and development expenses, interest income and income taxes.

AGIOS PHARMACEUTICALS, INC.

AMENDED AND RESTATED 2013 EMPLOYEE STOCK PURCHASE PLAN

Amended and Restated on December 2, 2024

The purpose of this Plan is to provide eligible employees of Agios Pharmaceuticals, Inc. (the "Company") and certain of its subsidiaries with opportunities to purchase shares of the Company's common stock, $0.001 par value (the "Common Stock"), commencing at such time as the Board of Directors of the Company (the "Board") shall determine. Subject to adjustment under Section 15 hereof, the number of shares of Common Stock that have been approved for this purpose is the sum of:

(a) three-hundred and twenty-seven thousand two-hundred and seventy-two (327,272) shares of Common Stock; plus

(b) an annual increase to be added on the first day of each fiscal year, commencing on January 1, 2014 and ending on December 31, 2023, equal to the lesser of (i) 509,091 shares of Common Stock, (ii) 1% of the outstanding shares on such date or (iii) an amount determined by the Board.

This Plan is intended to qualify as an "employee stock purchase plan" as defined in Section 423 of the Internal Revenue Code of 1986, as amended (the "Code"), and the regulations issued thereunder, and shall be interpreted consistent therewith.

1. Administration. The Plan will be administered by the Board or by a Committee appointed by the Board (the "Committee"). The Board or the Committee has authority to make rules and regulations for the administration of the Plan and its interpretation and decisions with regard thereto shall be final and conclusive.

2. Eligibility. All employees of the Company and all employees of any subsidiary of the Company (as defined in Section 424(f) of the Code) designated by the Board or the Committee from time to time (a "Designated Subsidiary"), are eligible to participate in any one or more of the offerings of Options (as defined in Section 9) to purchase Common Stock under the Plan provided that:

(a) they are customarily employed by the Company or a Designated Subsidiary for more than 20 hours a week and for more than five months in a calendar year; and

(b) they are employees of the Company or a Designated Subsidiary on the first day of the applicable Plan Period (as defined below).

No employee may be granted an Option hereunder if such employee, immediately after the Option is granted, owns 5% or more of the total combined voting power or value of the stock of the Company or any subsidiary. For purposes of the preceding sentence, the attribution rules of Section 424(d) of the Code shall apply in determining the stock ownership of an employee, and all stock that the employee has a contractual right to purchase shall be treated as stock owned by the employee.

The Company retains the discretion to determine which eligible employees may participate in an offering pursuant to and consistent with Treasury Regulation Sections 1.423-2(e) and (f).

3. Offerings. The Company will make one or more offerings ("Offerings") to employees to purchase stock under this Plan. Offerings will begin at such time as the Board shall determine. Each Offering will consist of a six-month period (a "Plan Period") during which payroll deductions will be made and held for the purchase of Common Stock at the end of the Plan Period. The Board or the Committee may, at its discretion, choose a different Plan Period of not more than twelve (12) months for Offerings.

4. Participation. An employee eligible on the first day of a Plan Period of any Offering may participate in such Offering by completing and forwarding either a written or electronic payroll deduction authorization form to the employee's appropriate payroll office at least 15 days prior to the commencement of the applicable Plan Period. The form will authorize a regular payroll deduction from the Compensation received by the employee during the Plan Period. Unless an employee files a new form or withdraws from the Plan, his deductions and purchases will continue at the same rate for future Offerings under the Plan as long as the Plan remains in effect. The term "Compensation"

means the employee's base salary reportable on the employee's Federal Income Tax Withholding Statement but including overtime and shift premium, and, in the case of salespersons, sales commissions to the extent determined by the Board or the Committee.

5. Deductions. The Company will maintain payroll deduction accounts for all participating employees. With respect to any Offering made under this Plan, an employee may authorize a payroll deduction in any percentage amount (in whole percentages) up to a maximum of 10.0% of the Compensation he or she receives during the Plan Period or such shorter period during which deductions from payroll are made. The Board or the Committee may, at its discretion, designate a lower maximum contribution rate. The minimum payroll deduction is such percentage of Compensation as may be established from time to time by the Board or the Committee.

6. Deduction Changes. An employee may decrease or discontinue his payroll deduction once during any Plan Period, by filing either a written or electronic new payroll deduction authorization form. However, an employee may not increase his payroll deduction during a Plan Period. If an employee elects to discontinue his payroll deductions during a Plan Period, but does not elect to withdraw his funds pursuant to Section 8 hereof, funds deducted prior to his election to discontinue will be applied to the purchase of Common Stock on the Exercise Date (as defined below).

7. Interest. Interest will not be paid on any employee accounts, except to the extent that the Board or the Committee, in its sole discretion, elects to credit employee accounts with interest at such rate as it may from time to time determine.

8. Withdrawal of Funds. An employee may at any time prior to the close of business on the fifteenth business day prior to the end of a Plan Period and for any reason permanently draw out the balance accumulated in the employee's account and thereby withdraw from participation in an Offering. Partial withdrawals are not permitted. The employee may not begin participation again during the remainder of the Plan Period during which the employee withdrew his or her balance. The employee may participate in any subsequent Offering in accordance with terms and conditions established by the Board or the Committee.

9. Purchase of Shares.

(a) Number of Shares. On the first day of each Plan Period, the Company will grant to each eligible employee who is then a participant in the Plan an option (an "Option") to purchase on the last business day of such Plan Period (the "Exercise Date") at the applicable purchase price (the "Option Price") up to that number of shares of Common Stock (which may include fractional shares) determined by multiplying $2,083 by the number of full months in the Plan Period and dividing the result by the closing price (as determined below) on the first day of such Plan Period; provided, however, that no employee may be granted an Option which permits his rights to purchase Common Stock under this Plan and any other employee stock purchase plan (as defined in Section 423(b) of the Code) of the Company and its subsidiaries, to accrue at a rate which exceeds $25,000 of the fair market value of such Common Stock (determined at the date such Option is granted) for each calendar year in which the Option is outstanding at any time; and, provided, further, however, that the Committee may, in its discretion, set a fixed maximum number of shares of Common Stock that each eligible employee may purchase per Plan Period which number may not be greater than the number of shares of Common Stock determined by using the formula in the first clause of this Section 9(a) and which number shall be subject to the second clause of this Section 9(b).

(b) Option Price. The Board or the Committee shall determine the Option Price for each Plan Period, including whether such Option Price shall be determined based on the lesser of the closing price of the Common Stock on (i) the first business day of the Plan Period or (ii) the Exercise Date, or shall be based solely on the closing price of the Common Stock on the Exercise Date; provided, however, that such Option Price shall be at least 85% of the applicable closing price. In the absence of a determination by the Board or the Committee, the Option Price will be 85% of the lesser of the closing price of the Common Stock on (i) the first business day of the Plan Period or (ii) the Exercise Date. The closing price shall be (a) the closing price (for the primary trading session) on any national securities exchange on which the Common Stock is listed or (b) the average of the closing bid and asked prices in the over-the-counter-market, whichever is applicable, as reported on the applicable stock exchange or trading

market. If no sales of Common Stock were made on such a day, the price of the Common Stock shall be the reported price for prior day on which sales were made.

(c) Exercise of Option. Each employee who continues to be a participant in the Plan on the Exercise Date shall be deemed to have exercised his Option at the Option Price on such date and shall be deemed to have purchased from the Company the number of whole shares of Common Stock reserved for the purpose of the Plan that his accumulated payroll deductions on such date will pay for, but not in excess of the maximum numbers determined in the manner set forth above.

(d) Return of Unused Payroll Deductions. Any balance remaining in an employee's payroll deduction account at the end of a Plan Period will be automatically refunded to the employee, except that any balance that is less than the purchase price of one share of Common Stock will be carried forward into the employee's payroll deduction account for the following Offering, unless the employee elects not to participate in the following Offering under the Plan, in which case the balance in the employee's account shall be refunded.

10. Issuance of Certificates. Certificates representing shares of Common Stock purchased under the Plan may be issued only in the name of the employee, in the name of the employee and another person of legal age as joint tenants with rights of survivorship, or (in the Company's sole discretion) in the name of a brokerage firm, bank, or other nominee holder designated by the employee. The Company may, in its sole discretion and in compliance with applicable laws, authorize the use of book entry registration of shares in lieu of issuing stock certificates.

11. Rights on Retirement, Death or Termination of Employment. If a participating employee's employment ends before the last business day of a Plan Period, no payroll deduction shall be taken from any pay then due and owing to the employee and the balance in the employee's account shall be paid to the employee. In the event of the employee's death before the last business day of a Plan Period, the Company shall, upon notification of such death, pay the balance of the employee's account (a) to the executor or administrator of the employee's estate or (b) if no such executor or administrator has been appointed to the knowledge of the Company, to such other person(s) as the Company may, in its discretion, designate. If, before the last business day of the Plan Period, the Designated Subsidiary by which an employee is employed ceases to be a subsidiary of the Company, or if the employee is transferred to a subsidiary of the Company that is not a Designated Subsidiary, the employee shall be deemed to have terminated employment for the purposes of this Plan.

12. Optionees Not Stockholders. Neither the granting of an Option to an employee nor the deductions from his or her pay shall make such employee a stockholder of the shares of Common Stock covered by an Option under this Plan until he or she has purchased and received such shares.

13. Options Not Transferable. Options under this Plan are not transferable by a participating employee other than by will or the laws of descent and distribution, and are exercisable during the employee's lifetime only by the employee.

14. Application of Funds. All funds received or held by the Company under this Plan may be combined with other corporate funds and may be used for any corporate purpose.

15. Adjustment for Changes in Common Stock and Certain Other Events.

(a) Changes in Capitalization. In the event of any stock split, reverse stock split, stock dividend, recapitalization, combination of shares, reclassification of shares, spin-off or other similar change in capitalization or event, or any dividend or distribution to holders of Common Stock other than an ordinary cash dividend, (i) the number and class of securities available under this Plan, (ii) the share limitations set forth in Section 9, and (iii) the Option Price shall be equitably adjusted to the extent determined by the Board or the Committee.

(b) Reorganization Events.

(1) Definition. A "Reorganization Event" shall mean: (a) any merger or consolidation of the Company with or into another entity as a result of which all of the Common Stock of the Company is converted into or exchanged for the right to receive cash, securities or other property or is cancelled, (b) any transfer or disposition of all of the Common

Stock of the Company for cash, securities or other property pursuant to a share exchange or other transaction or (c) any liquidation or dissolution of the Company.

(2) Consequences of a Reorganization Event on Options. In connection with a Reorganization Event, the Board or the Committee may take any one or more of the following actions as to outstanding Options on such terms as the Board or the Committee determines: (i) provide that Options shall be assumed, or substantially equivalent Options shall be substituted, by the acquiring or succeeding corporation (or an affiliate thereof), (ii) upon written notice to employees, provide that all outstanding Options will be terminated immediately prior to the consummation of such Reorganization Event and that all such outstanding Options will become exercisable to the extent of accumulated payroll deductions as of a date specified by the Board or the Committee in such notice, which date shall not be less than ten (10) days preceding the effective date of the Reorganization Event, (iii) upon written notice to employees, provide that all outstanding Options will be cancelled as of a date prior to the effective date of the Reorganization Event and that all accumulated payroll deductions will be returned to participating employees on such date, (iv) in the event of a Reorganization Event under the terms of which holders of Common Stock will receive upon consummation thereof a cash payment for each share surrendered in the Reorganization Event (the "Acquisition Price"), change the last day of the Plan Period to be the date of the consummation of the Reorganization Event and make or provide for a cash payment to each employee equal to (A) (1) the Acquisition Price times (2) the number of shares of Common Stock that the employee's accumulated payroll deductions as of immediately prior to the Reorganization Event could purchase at the Option Price, where the Acquisition Price is treated as the fair market value of the Common Stock on the last day of the applicable Plan Period for purposes of determining the Option Price under Section 9(b) hereof, and where the number of shares that could be purchased is subject to the limitations set forth in Section 9(a), minus (B) the result of multiplying such number of shares by such Option Price, (v) provide that, in connection with a liquidation or dissolution of the Company, Options shall convert into the right to receive liquidation proceeds (net of the Option Price thereof) and (vi) any combination of the foregoing.

For purposes of clause (i) above, an Option shall be considered assumed if, following consummation of the Reorganization Event, the Option confers the right to purchase, for each share of Common Stock subject to the Option immediately prior to the consummation of the Reorganization Event, the consideration (whether cash, securities or other property) received as a result of the Reorganization Event by holders of Common Stock for each share of Common Stock held immediately prior to the consummation of the Reorganization Event (and if holders were offered a choice of consideration, the type of consideration chosen by the holders of a majority of the outstanding shares of Common Stock); provided, however, that if the consideration received as a result of the Reorganization Event is not solely common stock of the acquiring or succeeding corporation (or an affiliate thereof), the Company may, with the consent of the acquiring or succeeding corporation, provide for the consideration to be received upon the exercise of Options to consist solely of such number of shares of common stock of the acquiring or succeeding corporation (or an affiliate thereof) that the Board determines to be equivalent in value (as of the date of such determination or another date specified by the Board) to the per share consideration received by holders of outstanding shares of Common Stock as a result of the Reorganization Event.

16. Amendment of the Plan. The Board may at any time, and from time to time, amend or suspend this Plan or any portion thereof, except that (a) if the approval of any such amendment by the shareholders of the Company is required by Section 423 of the Code, such amendment shall not be effected without such approval, and (b) in no event may any amendment be made that would cause the Plan to fail to comply with Section 423 of the Code.

17. Insufficient Shares. If the total number of shares of Common Stock specified in elections to be purchased under any Offering plus the number of shares purchased under previous Offerings under this Plan exceeds the maximum number of shares issuable under this Plan, the Board or the Committee will allot the shares then available on a pro-rata basis.

18. Termination of the Plan. This Plan may be terminated at any time by the Board. Upon termination of this Plan all amounts in the accounts of participating employees shall be promptly refunded.

19. Governmental Regulations. The Company's obligation to sell and deliver Common Stock under this Plan is subject to listing on a national stock exchange (to the extent the Common Stock is then so listed or quoted) and the

approval of all governmental authorities required in connection with the authorization, issuance or sale of such stock.

20. Governing Law. The Plan shall be governed by Delaware law except to the extent that such law is preempted by federal law.

21. Issuance of Shares. Shares may be issued upon exercise of an Option from authorized but unissued Common Stock, from shares held in the treasury of the Company, or from any other proper source.

22. Notification upon Sale of Shares. Each employee agrees, by entering the Plan, to promptly give the Company notice of any disposition of shares purchased under the Plan where such disposition occurs within two years after the date of grant of the Option pursuant to which such shares were purchased.

23. Grants to Employees in Foreign Jurisdictions. The Company may, to comply with the laws of a foreign jurisdiction, grant Options to employees of the Company or a Designated Subsidiary who are citizens or residents of such foreign jurisdiction (without regard to whether they are also citizens of the United States or resident aliens (within the meaning of Section 7701(b)(1)(A) of the Code)) with terms that are less favorable (but not more favorable) than the terms of Options granted under the Plan to employees of the Company or a Designated Subsidiary who are resident in the United States. Notwithstanding the preceding provisions of this Plan, employees of the Company or a Designated Subsidiary who are citizens or residents of a foreign jurisdiction (without regard to whether they are also citizens of the United States or resident aliens (within the meaning of Section 7701(b)(1)(A) of the Code)) may be excluded from eligibility under the Plan if (a) the grant of an Option under the Plan to a citizen or resident of the foreign jurisdiction is prohibited under the laws of such jurisdiction or (b) compliance with the laws of the foreign jurisdiction would cause the Plan to violate the requirements of Section 423 of the Code. The Company may add one or more appendices to this Plan describing the operation of the Plan in those foreign jurisdictions in which employees are excluded from participation or granted less favorable Options.

24. Authorization of Sub-Plans. The Board may from time to time establish one or more sub-plans under the Plan with respect to one or more Designated Subsidiaries, provided that such sub-plan complies with Section 423 of the Code.

25. Withholding. If applicable tax laws impose a tax withholding obligation, each affected employee shall, no later than the date of the event creating the tax liability, make provision satisfactory to the Board for payment of any taxes required by law to be withheld in connection with any transaction related to Options granted to or shares acquired by such employee pursuant to the Plan. The Company may, to the extent permitted by law, deduct any such taxes from any payment of any kind otherwise due to an employee.

26. Effective Date and Approval of Shareholders. The Plan shall take effect on June 15, 2013 subject to approval by the shareholders of the Company as required by Section 423 of the Code, which approval must occur within twelve months of the adoption of the Plan by the Board.

2013 Employee Stock Purchase Plan adopted by the Board of Directors

on June 15, 2013

And approved by the stockholders on June 17, 2013

Amendment and Restatement of 2013 Employee Stock Purchase Plan approved by the Board of Directors on December 2, 2024

Agios Pharmaceuticals, Inc.

Insider Trading Policy

Adopted by the Board of Directors on March 2, 2023

Effective March 3, 2023

1. Background and Purpose

1.1 Why Have We Adopted This Policy?

The federal securities laws prohibit any member of the Board of Directors (a "Director"), officer (as defined in Rule 16a-1(f) under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), an "executive officer") or employee of Agios Pharmaceuticals, Inc. (together with its subsidiaries, the "Company") from purchasing or selling Company securities on the basis of material nonpublic information concerning the Company, or from tipping material nonpublic information to others. These laws impose severe sanctions on individuals who violate them. In addition, the Securities and Exchange Commission (the "SEC") has the authority to impose large fines on the Company and on the Company's Directors, executive officers and controlling stockholders if the Company's employees engage in insider trading and the Company has failed to take appropriate steps to prevent it (so-called "controlling person" liability).

This insider trading policy is being adopted in light of these legal requirements, and with the goal of helping:

- prevent inadvertent violations of the insider trading laws;
- avoid embarrassing proxy disclosure of reporting violations by persons subject to Section 16 of the Exchange Act;
- promote compliance with the Company's obligation to publicly disclose information related to its insider trading policies and practices and the use of certain trading arrangements by Company insiders;
- avoid even the appearance of impropriety on the part of those employed by, or associated with, the Company;
- protect the Company from controlling person liability; and
- protect the reputation of the Company, its Directors and its employees.

The provisions in Sections 2 and 3 of this policy are not applicable to transactions by the Company itself. Transactions by the Company will comply with applicable U.S. federal securities laws, including those relating to insider trading.

1.2 What Type of Information is "Material"?

Information concerning the Company is considered material if there is a substantial likelihood that a reasonable shareholder would consider the information important in making an

investment decision with respect to the Company's securities. Stated another way, there must be a substantial likelihood that a reasonable shareholder would view the information as having significantly altered the "total mix" of information available about the Company. Material information can include positive or negative information about the Company. Information concerning any of the following subjects, or the Company's plans with respect to any of these subjects, would often be considered material:

- the Company's liquidity, cash burn rate, revenues or earnings;
- a significant merger or acquisition involving the Company;
- a change in control of the Company;
- a significant licensing or collaboration agreement or serious discussions regarding such an agreement;
- a significant change in management or the Board of Directors of the Company;
- the Company's decision to commence or terminate the payment of cash dividends;
- the public or private sale of a significant amount of securities of the Company;
- the establishment of a program to repurchase securities of the Company;
- a stock split;
- a default on outstanding debt or preferred stock of the Company or a bankruptcy filing;
- a new product release or a significant development, invention or discovery;
- information concerning significant clinical trials, including the timing of and findings and data from such trials;
- information concerning upcoming FDA actions or other significant regulatory developments, including a significant product recall;
- the loss, delay or gain of a significant contract, sale or order or other important development regarding customers, collaborators or suppliers;
- a significant cybersecurity incident or investigation of a potential such incident;
- a conclusion by the Company or a notification from its independent auditor that any of the Company's previously issued financial statements should no longer be relied upon; or
- a change in or dispute with the Company's independent auditor.

This list is illustrative only and is not intended to provide a comprehensive list of circumstances that could give rise to material information.

1.3 When is Information "Nonpublic"?

Information concerning the Company is considered nonpublic if it has not been disseminated in a manner making it available to investors generally.

Information will generally be considered nonpublic unless (1) the information has been disclosed in a press release, in a public filing made with the SEC (such as a Report on Form 10-K, Form 10-Q or Form 8-K), or through a news wire service or daily newspaper of wide circulation, and (2) a sufficient amount of time has passed so that the information has had an opportunity to be digested by the marketplace.

2. Prohibitions Relating to Transactions in the Company's Securities

2.1 Covered Persons. This Section 2 applies to:

- all Directors;
- all employees;
- all family members of Directors and employees who share the same address as, or are financially dependent on, the Director or employee and any other person who shares the same address as the Director or employee (other than (x) an employee or tenant of the Director or employee or (y) another unrelated person whom the Chief Legal Officer determines should not be covered by this policy); and
- all corporations, limited liability companies, partnerships, trusts or other entities controlled by any of the above persons, unless the entity has implemented policies or procedures designed to ensure that such person cannot influence transactions by the entity involving Company securities.

2.2 Prohibition on Trading While Aware of Material Nonpublic Information.

(a) Prohibited Activities. Except as provided in Section 4, no person or entity covered by Section 2 may:

- Purchase, sell or donate any securities of the Company while he or she is aware of any material nonpublic information concerning the Company or recommend to another person that they do so;
- Tip or otherwise disclose to any other person any material nonpublic information concerning the Company if such person may misuse that information, such as by purchasing or selling Company securities or tipping that information to others;
- Purchase, sell or donate any securities of another company while he or she is aware of any material nonpublic information concerning such other company which he or she learned in the course of his or her service as a Director or employee of the Company or recommend to another person that they do so; or

- disclose to any other person any material nonpublic information concerning another company which he or she learned in the course of his or her service as a Director or employee of the Company if such person may misuse that information, such as by purchasing or selling securities of such other company or tipping that information to others.

(b) Application of Policy After Cessation of Service. If a person ceases to be a Director or employee of the Company at a time when he or she is aware of material nonpublic information concerning the Company, the prohibition on purchases, sales or donations of Company securities in Section 2.2(a) shall continue to apply to such person until that information has become public or is no longer material.

2.3 Prohibition on Pledges. No person or entity covered by this Section 2 may purchase Company securities on margin, borrow against Company securities held in a margin account, or pledge Company securities as collateral for a loan. However, an exception may be granted in extraordinary situations where a person wishes to pledge Company securities as collateral for a loan (other than a margin loan) and clearly demonstrates the financial capacity to repay the loan without resort to the pledged securities. Any person who wishes to pledge Company securities as collateral for a loan must submit a request for approval to the Chief Financial Officer or Chief Legal Officer. In addition, any such request by a director or executive officer must also be reviewed and approved by the Audit Committee.

2.4 Prohibition on Short Sales, Derivative Transactions and Hedging Transactions. No person or entity covered by this Section 2 may engage in any of the following types of transactions with respect to Company securities:

- short sales, including short sales "against the box"; or
- purchases or sales of puts, calls or other derivative securities ; or
- purchases of financial instruments (including prepaid variable forward contracts, equity swaps, collars and exchange funds) or other transactions that hedge or offset, or are designed to hedge or offset, any decrease in the market value of Company securities.

3. Additional Prohibitions Applicable to Directors, Executive Officers and Designated Employees

3.1 Covered Persons. This Section 3 applies to:

- all Directors;
- all executive officers;
- such other employees as are designated from time to time by the Board of Directors, the Chief Executive Officer, the Chief Financial Officer or the Chief Legal Officer, as being subject to this Section 3 (the "Designated Employees");
- all family members of Directors, executive officers and Designated Employees who share the same address as, or are financially dependent on, the Director, executive officer or Designated Employee and any other person who shares the same address as the Director, executive officer or Designated Employee (other than (x) an employee or tenant of the Director, executive officer or Designated

Employee or (y) another unrelated person whom the Chief Legal Officer determines should not be covered by this policy); and

- all corporations, limited liability companies, partnerships, trusts or other entities controlled by any of the above persons, unless the entity has implemented policies or procedures designed to ensure that such person cannot influence transactions by the entity involving Company securities.

3.2 Blackout Periods**.**

(a) Regular Blackout Periods. Except as provided in Section 4, no person or entity covered by this Section 3 may purchase, sell or donate any securities of the Company during the period beginning on the fifteenth day of the last month of each fiscal quarter and ending upon the completion of the second full trading day after the public announcement of earnings for such quarter (a "regular blackout period").

(b) Corporate News Blackout Periods. The Company may from time to time notify Directors, executive officers and other specified employees that an additional blackout period (a "corporate news blackout period") is in effect in view of significant events or developments involving the Company. In such event, except as provided in Section 4, no such individual may purchase, sell or donate any securities of the Company during such corporate news blackout period or inform anyone else that a corporate news blackout period is in effect. (In this policy, regular blackout periods and corporate news blackout periods are each referred to as a "blackout period.")

(c) Awareness of Material Non-Public Information when a Blackout Period is Not in Effect. The prohibitions set forth in Section 2.2(a) with respect to transactions made by persons or entities while aware of material nonpublic information apply regardless of whether a blackout period is then in effect.

3.3 Notice and Pre-Clearance of Transactions**.**

(a) Pre-Transaction Clearance. No person or entity covered by this Section 3 (a "Pre-Clearance Person") may purchase, sell, donate, transfer or otherwise acquire or dispose of securities of the Company, either directly or indirectly, other than in a transaction permitted under Section 4, unless such person pre-clears the transaction with either the Chief Financial Officer or the Chief Legal Officer. A request for pre-clearance shall be made in accordance with the procedures established by the Chief Legal Officer. A request for pre-clearance may be oral or in writing (including by email), should be made at least two business days in advance of the proposed transaction and should include the identity of the Pre-Clearance Person, the type of proposed transaction (for example, an open market purchase, a privately negotiated sale, an option exercise, etc.), the proposed date of the transaction and the number of options or shares to be involved. In addition, the Pre-Clearance person must execute a certification (in the form approved by the Chief Legal Officer) that he, she or it is not aware of material nonpublic information about the Company. The Chief Financial Officer and the Chief Legal Officer shall have sole discretion to decide whether to clear any contemplated transaction. (The Chief Legal Officer shall have sole discretion to decide whether to clear transactions by the Chief Financial Officer or persons or entities subject to this policy as a result of their relationship with the Chief Financial Officer, and the Chief Financial Officer shall have sole discretion to decide whether to clear transactions by the Chief Legal Officer or persons or entities subject to this policy as a result of their relationship with the Chief Legal Officer) All transactions that are pre-cleared must be effected within three business days of receipt of the pre-clearance unless a longer or shorter period has been specified by the Chief Financial Officer or the Chief Legal Officer. A pre-cleared transaction (or any portion of a pre-cleared transaction) that has not been effected

during the three business day period must be pre-cleared again prior to execution. Notwithstanding receipt of pre-clearance, if the Pre-Clearance Person becomes aware of material non-public information or becomes subject to a blackout period before the transaction is effected, the transaction may not be completed.

(b) Post-Transaction Notice. Each person or entity covered by this Section 3 who is subject to reporting obligations under Section 16 of the Exchange Act shall also notify the Chief Financial Officer or the Chief Legal Officer (or his or her respective designee) of the occurrence of any purchase, sale, donation, transfer or other acquisition or disposition of securities of the Company as soon as possible following the transaction, but in any event within one business day after the transaction. Such notification may be oral or in writing (including by e-mail) and should include the identity of the covered person, the type of transaction, the date of the transaction, the number of shares involved, the purchase or sale price, and whether the transaction was effected pursuant to a contract, instruction or written plan that is intended either to satisfy the affirmative defense conditions of Rule 10b5-1(c) or to constitute a non-Rule 10b5-1 trading arrangement (as defined in Item 408(c) of Regulation S-K).

(c) Deemed Time of a Transaction. For purposes of this Section 3.3, a purchase, sale, donation, transfer or other acquisition or disposition shall be deemed to occur at the time the person becomes irrevocably committed to it (for example, in the case of an open market purchase or sale, this occurs when the trade is executed, not when it settles).

4. **Exceptions.**

4.1 Exceptions. The prohibitions in Sections 2.2(a) and 3.2 on purchases, sales and donations of Company securities do not apply to:

- exercises of stock options or other equity awards or the surrender of shares to the Company in payment of the exercise price or in satisfaction of any tax withholding obligations, in each case in a manner permitted by the applicable equity award agreement; provided, however, that the securities so acquired may not be sold (either outright or in connection with a "cashless" exercise transaction through a broker) while the employee or Director is aware of material nonpublic information or, in the case of someone who is subject to Section 3, during a blackout period (as defined in Section 2.3(b));

- acquisitions or dispositions of Company common stock under the Company's 401(k) or other individual account plan that are made pursuant to standing instructions, in a form approved by the Company, not entered into or modified while the employee or Director is aware of material nonpublic information or, in the case of someone who is subject to Section 3, during a blackout period;

- other purchases of securities from the Company (including purchases under the Company's Employee Stock Purchase Plan) or sales of securities to the Company;

- bona fide gifts that are approved in advance by the Company; and

- purchases, sales or donations made pursuant to a binding contract, written plan or specific instruction which satisfies the applicable affirmative defense

conditions of Rule 10b5-1(c), including as applicable the requirements applicable to an eligible sell-to-cover transaction as defined in Rule 10b5-1(c)(1)(ii)(D)(3)), or for which the affirmative defense is available under Rule 10b5-1(c) because such plan was adopted prior to February 27, 2023, met the affirmative defense conditions in effect at the time of adoption, and was not modified or changed on or after February 27, 2023 (a "trading plan"); provided such trading plan: (1) is in writing; and (2) was submitted to the Company for review by the Company prior to its adoption; and

- purchases, sales or donations made pursuant to a binding contract, written plan or specific instruction which satisfies the definition of a "non-Rule 10b5-1 trading arrangement as such term is defined in Item 408(c) of Regulation S-K, provided such non-Rule 10b5-1 trading arrangement: (1) is in writing and (2) was submitted to the Company for review prior to its adoption.

4.2 Partnership Distributions. Nothing in this policy is intended to limit the ability of a venture capital partnership or other similar entity with which a Director is affiliated to distribute Company securities to its partners, members or other similar persons. It is the responsibility of each affected Director and the affiliated entity, in consultation with their own counsel (as appropriate), to determine the timing of any distributions, based on all relevant facts and circumstances and applicable securities laws.

4.3 Underwritten Public Offering. Nothing in this policy is intended to limit the ability of any person to sell Company securities as a selling stockholder in an underwritten public offering pursuant to an effective registration statement in accordance with applicable securities law.

5. **Regulation BTR**

If the Company is required to impose a "pension fund blackout period" under Regulation BTR, each Director and executive officer shall not, directly or indirectly sell, purchase or otherwise transfer during such blackout period any equity securities of the Company acquired in connection with his or her service as a director or officer of the Company, except as permitted by Regulation BTR.

6. **Penalties for Violation**

Violation of any of the foregoing rules is grounds for disciplinary action by the Company, including termination of employment. In addition to any disciplinary actions the Company may take, insider trading can also result in administrative, civil or criminal proceedings which can result in significant fines and civil penalties, being barred from service as an officer or director of a public company, or imprisonment.

7. **Company Assistance and Education**

7.1 Education. The Company shall take reasonable steps designed to ensure that all Directors and employees of the Company are educated about, and periodically reminded of, the federal securities law restrictions and Company policies regarding insider trading.

7.2 Assistance. The Company shall provide reasonable assistance to all Directors and executive officers, as requested by such Directors and executive officers, in connection with the filing of Forms 3, 4 and 5 under Section 16 of the Exchange Act. However, the ultimate responsibility, and liability, for timely filing remains with the Directors and executive officers.

7.3 Limitation on Liability. None of the Company, the Chief Financial Officer, the Chief Legal Officer or the Company's other employees will have any liability for any delay in reviewing, or refusal of, a request to allow a pledge submitted pursuant to Section 2.3, a request for pre-clearance submitted pursuant to Section 3.3(a) or a trading plan submitted pursuant to Section 4.1. Notwithstanding any pre-clearance of a transaction pursuant to Section 3.3(a) or review of a trading plan pursuant to Section 4.1, none of the Company, the Chief Financial Officer, the Chief Legal Officer or the Company's other employees, assumes any liability for the legality or consequences of such transaction or trading plan to the person engaging in or adopting such transaction or trading plan.

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. 333-272615, 333-269951, 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.333-269949) of Agios Pharmaceuticals, Inc. of our report dated February 13, 2025 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 13, 2025

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 13, 2025

/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 13, 2025

/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, 2024, 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 13, 2025

/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, 2024, 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 13, 2025

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