UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2022

or

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

For the transition period from to

Commission File No. 001-37852

PROTAGONIST THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**98-0505495**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
7707 Gateway Boulevard, Suite 140 Newark, California 94560	
(Address, including zip code, of registrant's principal executive offices)	**(510) 474-0170 (Telephone number, including area code, of registrant's principal executive offices)**

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

Title of each class	**Trading Symbol**	**Name of each exchange on which registered**
Common Stock, $0.00001 par value	**PTGX**	**The Nasdaq Stock Market LLC**

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. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act of 1934). Yes ☐ No ☒

The aggregate market value of the voting stock held by non-affiliates of the registrant was approximately $379.5 million as of June 30, 2022, based upon the closing sale price on The Nasdaq Stock Market LLC reported on June 30, 2022. Excludes an aggregate of 706,756 shares of the registrant's common stock held by officers, directors and affiliated stockholders. For purposes of determining whether a stockholder was an affiliate of the registrant at June 30, 2022, the registrant assumed that a stockholder was an affiliate of the registrant at June 30, 2022 if such stockholder (i) beneficially owned 10% or more of the registrant's common stock, as determined based on public filings and/or (ii) was an executive officer or director or was affiliated with an executive officer or director of the registrant at June 30, 2022. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

There were 51,275,166 shares of registrant's Common Stock, par value $0.00001 per share, outstanding as of March 2, 2023.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant's definitive Proxy Statement for the registrant's 2023 Annual Meeting of Stockholders are incorporated by reference into Part III of this report. Such proxy statement will be filed with the Securities and Exchange Commission within 120 days after the end of the registrant's fiscal year ended December 31, 2022.

Auditor Firm ID:	42	Auditor Name:	Ernst & Young LLP	Auditor Location:	San Mateo, California, USA

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PART I

Statements made in this Annual Report on Form 10-K contain certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. Forward-looking statements are identified by words such as "believe," "will," "may," "estimate," "continue," "anticipate," "intend," "should," "plan," "expect," "predict," "forecast," "target," "could," "would," "potentially" or the negative of these terms or similar expressions. You should read these statements carefully because they discuss current expectations about future events, contain projections of future results of operations or financial condition, or state other "forward-looking" information. In addition, any statements other than statements of historical facts are forward-looking statements. These statements relate to our plans, objectives, goals, targets, expectations, intentions, priorities and projections of financial performance and the assumptions that underlie these statements. These forward-looking statements are subject to certain known and unknown risks, uncertainties and other factors that could cause actual results to differ materially from those anticipated in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those discussed in this report below, in "Item 1A. Risk Factors" and elsewhere in this Annual Report. In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements. Forward-looking statements are based on our management's belief, estimates and assumptions and on information currently available to our management. These statements, like all statements in this report, speak only as of their date, and except as required by law, we undertake no obligation to update or revise these statements in light of future developments. We caution investors that our business and financial performance are subject to substantial risks and uncertainties.

Summary of Risk Factors

Below is a summary of the principal factors that make an investment in our common stock speculative or risky. This summary does not address all of the risks that we face. Additional discussion of the risks summarized in this risk factor summary, and other risks that we face, can be found below under the heading "Item 1A. Risk Factors" and should be carefully considered, together with other information in this Annual Report on Form 10-K and our other filings with the SEC, before making an investment decision regarding our common stock.

- We have no approved products and no historical commercial revenue, which makes it difficult to assess our future prospects and financial results.
- We are heavily dependent on the success of our product candidates in clinical development.
- Clinical development is a lengthy and expensive process with an uncertain outcome, and failure can occur at any stage of clinical development.
- Our product candidates may cause undesirable side effects or have other properties adversely impacting safety that delay or prevent their regulatory approval, restrict their approved labeling, or otherwise limit their commercial opportunity, including being required by an independent data monitoring committee or regulatory authorities to, delay or halt or clinical trials, or if such side effects or adverse events are sufficiently severe or prevalent, order us to suspend or cease altogether further development of our product candidates.
- We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future.
- We have never generated any revenue from product sales and may never be profitable.

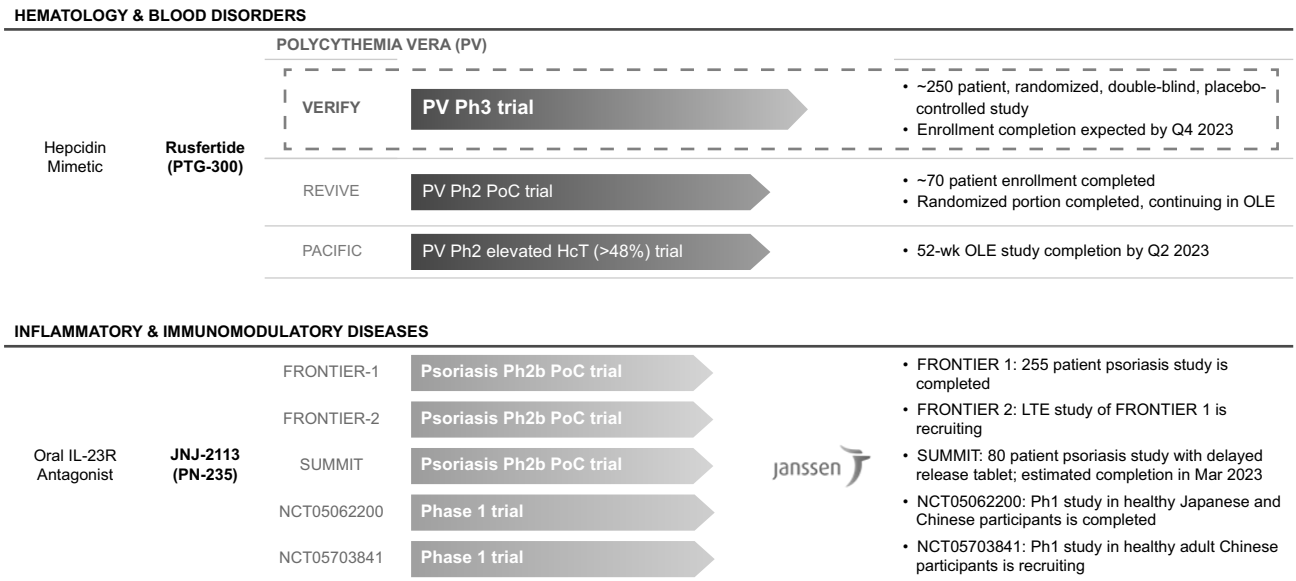
- We expect to require substantial additional funding.
- Raising additional capital may cause dilution to our existing stockholders.
- We rely on Janssen Biotech, Inc. ("Janssen") to continue the development of product candidates subject to our license and collaboration with Janssen, and to successfully commercialize any resulting products.
- Our existing or future collaborations with third parties may not be successful.
- We rely on third parties to conduct our pre-clinical studies and clinical trials and are subject to risks associated with their businesses and performance of their obligations to us.
- We rely on third-party contract manufacturers to manufacture our drug substance and clinical drug product.
- If we are ultimately unable to obtain regulatory approval for our product candidates in the United States or other jurisdictions, our business will be substantially harmed.
- We have no marketing and sales organization and may not be able to effectively market and sell any products or generate product revenue if any of our product candidates are approved for marketing.
- If we commercialize our product candidates abroad, we will be subject to the risks of doing business outside of the United States.
- We face significant competition from other biotechnology and pharmaceutical companies.
- We face risks to our business arising from the COVID-19 pandemic, including risks to our ongoing and planned clinical trials and pre-clinical and discovery research.
- Unstable market and economic conditions, including elevated and sustained inflation, may have serious adverse consequences on our business, financial condition and stock price.
- Our success depends on our ability to attract, retain and motivate qualified executives and other personnel.
- We may experience difficulties in managing the growth of our organization.
- We are subject to risks associated with information technology systems or breaches of data security.
- Any misconduct by our employees, independent contractors, principal investigators, consultants and vendors could have a material adverse effect on our business.
- Our headquarters is located near known earthquake fault zones.
- If we are unable to obtain or protect intellectual property rights related to our product candidates and technologies, we may not be able to compete effectively in our markets.
- We may be involved in lawsuits to protect or enforce our intellectual property, which could be expensive, time consuming and ultimately unsuccessful.
- Patents covering our product candidates could be found invalid or unenforceable.
- Third party claims of intellectual property infringement may prevent or delay our drug discovery and development efforts.
- Our stock price has been and will likely continue to be volatile and may decline, regardless of our operating performance.

Item 1. Business

Overview

We are a biopharmaceutical company with peptide-based new chemical entities rusfertide and JNJ-2113 (formerly known as PN-235) in different stages of development, all derived from our proprietary discovery technology platform. Our clinical programs fall into two broad categories of diseases; (i) hematology and blood disorders, and (ii) inflammatory and immunomodulatory diseases.

Figure 1: Our Product Pipeline



Rusfertide

Our most advanced clinical asset, rusfertide (generic name for PTG-300), is an injectable hepcidin mimetic in development for the potential treatment of erythrocytosis, iron overload and other blood disorders and is wholly owned. Hepcidin is a key hormone in regulating iron equilibrium and is critical to the proper development of red blood cells. Rusfertide mimics the effect of the natural hormone hepcidin, but with greater potency, solubility and stability. Data from our rusfertide Phase 2 clinical trials presented at medical conferences in 2021 and 2022 provided evidence regarding the potential of rusfertide for managing hematocrit, reducing thrombotic risk and improving iron deficiency symptoms. Rusfertide has a unique mechanism of action in the potential treatment of the blood disorder polycythemia vera ("PV"), which may enable it to specifically decrease and maintain hematocrit levels within the range of recommended clinical guidelines without causing the iron deficiency that can occur with frequent phlebotomy. Our rusfertide Phase 2 clinical trials include the following:

- REVIVE, a Phase 2 proof of concept ("POC") trial, was initiated in the fourth quarter of 2019. We completed enrollment of patients in the first quarter of 2022 with a target of approximately 50 patients to be enrolled through the end of the randomization portion of the trial, which was completed during the first quarter of 2023, and will continue in open label extension.

- PACIFIC, another Phase 2 trial for rusfertide patients diagnosed with PV and with routinely elevated hematocrit levels (>48%), was initiated during the first quarter of 2021 and completion of the 52-week trial is expected during the second quarter of 2023.

At the June 2022 American Society of Clinical Oncology ("ASCO") Annual Meeting, we presented updated interim results for REVIVE and PACIFIC demonstrating the effects of dosing interruption and resumption. Rusfertide dosing interruption led to loss of effect, including increased phlebotomy rate and increases in hematocrit and red blood cells. Rusfertide restart restored therapeutic benefits. Following the brief clinical hold described below, over 90% of patients in the REVIVE trial provided reconsent and returned to rusfertide treatment after dosing interruption and reinitiation. At the June 2022 European Hematology Association Congress, we presented interim data as of May 2022 showing that rusfertide treatment interruption reverses hematologic gains and re-initiation of treatment restores therapeutic benefits in patients with PV. At the December 2022 American Society of Hematology ("ASH") meeting, we presented data as of October 2022 related to rusfertide, including a subgroup of analyses of the adverse event profile from the REVIVE trial. These preliminary results indicated that 84% of treatment-emergent adverse events ("TEAEs") were Grade 2 or below. 16% of patients experienced Grade 3 TEAEs and there were no Grade 4 TEAEs.

On March 15, 2023, we announced positive topline results from the blinded, placebo-controlled, randomized withdrawal portion of the REVIVE trial. Subjects receiving rusfertide achieved statistically significant improvements versus placebo in the trial's primary endpoint.

The double-blind, placebo-controlled, 12-week randomized withdrawal portion was included as Part 2 of the REVIVE trial study to evaluate rusfertide in PV patients with frequent phlebotomy requirements. In the REVIVE trial, subjects were initially enrolled in the 28-week open label dose-titration and efficacy evaluation Part 1 of the study, followed by 1:1 randomization of 53 subjects to placebo versus rusfertide therapy for a subsequent duration of 12 weeks. More subjects receiving rusfertide during the blinded randomized withdrawal portion of the REVIVE trial were responders compared with placebo (69.2% versus 18.5%, p=0.0003). A study subject was defined as a responder if the subject completed 12 weeks of double-blind treatment while maintaining hematocrit control without phlebotomy eligibility and without phlebotomy. During the 12 weeks of the blinded randomized withdrawal, only 2 of 26 subjects on rusfertide were phlebotomized.

VERIFY, a global Phase 3 clinical trial of rusfertide in PV for approximately 250 patients, was initiated in the first quarter of 2022. Significant efforts have been taken toward the goal of full enrollment and a high degree of interest has been observed from physicians and patient communities. We expect enrollment completion in the fourth quarter of 2023.

On September 16, 2021, the U.S. Food and Drug Administration ("FDA") placed a clinical hold on our then ongoing rusfertide clinical trials following our submission to the FDA of findings in a 26-week rasH2 transgenic mouse carcinogenicity study. In October 2021, we submitted a Complete Response to the FDA related to the clinical hold, and the FDA removed the clinical hold on October 8, 2021. In our Complete Response, we provided the individual patient clinical safety reports the FDA requested for human cancers observed in rusfertide clinical trials, updated the investigator brochure and patient informed consent forms for ongoing rusfertide trials, proposed new safety and stopping rules in trial protocols for our ongoing rusfertide clinical trials, and performed a comprehensive review of our rusfertide safety database. Dosing of patients and enrollment in ongoing clinical trials with rusfertide resumed in the fourth quarter of 2021.

The FDA granted orphan drug designation for rusfertide for the treatment of PV in June 2020, and Fast Track designation for rusfertide for the treatment of PV in December 2020. The EMA granted orphan drug designation for rusfertide for treatment of PV in October 2020. The FDA granted Breakthrough Therapy Designation for rusfertide for the treatment of PV in June 2021. In April 2022, we received a letter from the FDA indicating the FDA's intent to rescind Breakthrough Therapy Designation for rusfertide in PV. In June 2022, we voluntarily withdrew our Breakthrough Therapy Designation following correspondence with FDA and based on our internal analysis of the relative utility of Breakthrough Therapy Designation for Phase 3 trials and beyond. The FDA correspondence relating to the Breakthrough Therapy designation does not address the rusfertide Fast Track Designation, which remains active.

In keeping with our organizational prioritization of rusfertide in PV, plans to initiate trials of rusfertide in additional disease indications have been paused. This decision was influenced in part by the enactment of the Inflation Reduction Act ("IRA") in the United States and includes previously planned trials of rusfertide in the subset of hereditary hemochromatosis patients with chronic arthropathy.

JNJ-2113 (formerly known as PN-235)

Our partnered Interleukin-23 receptor ("IL-23R") antagonist compound JNJ-2113 is an orally delivered investigational drug that is designed to block biological pathways currently targeted by marketed injectable antibody drugs. Our orally stable peptide approach may offer a targeted therapeutic approach for gastrointestinal ("GI") and systemic compartments as needed. We believe that, compared to antibody drugs, JNJ-2113 has the potential to provide clinical improvement in an oral medication with increased convenience and compliance and the opportunity for the earlier introduction of targeted oral therapy.

In May 2017, we entered into a worldwide license and collaboration agreement with Janssen Biotech, Inc. ("Janssen"), a Johnson & Johnson company, to co-develop and co-detail our IL-23R antagonist compounds, including PTG-200 (JNJ-67864238) and certain related compounds for all indications, including inflammatory bowel disease ("IBD"). PTG-200 was a first-generation investigational, orally delivered, IL-23R antagonist for the treatment of IBD. The agreement with Janssen was amended in May 2019 to expand the collaboration by supporting efforts towards second-generation IL-23R antagonists; and in July 2021 to, among other things, enable Janssen to independently research and develop collaboration compounds for multiple indications in the IL-23 pathway and further align our financial interests.

During the fourth quarter of 2021, following a pre-specified interim analysis criteria, a portfolio decision was made by Janssen to advance second-generation product candidate JNJ-2113 (JNJ-77242113) based on its superior potency and overall pharmacokinetic and pharmacodynamic profile. A JNJ-2113 Phase 1 trial was completed in the fourth quarter of 2021.

In February 2022, Janssen initiated FRONTIER1, a 255-patient Phase 2b clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis, which was completed in December 2022. FRONTIER1 was a randomized, multicenter, double-blind, placebo-controlled study that evaluated three once-daily dosages and two twice-daily dosages of JNJ-2113 taken orally. The primary endpoint of the study is the proportion of patients achieving PASI-75 (a 75% improvement in skin lesions as measured by the Psoriasis Area and Severity Index) at 16 weeks. In March 2023, we announced positive topline results from the trial. JNJ-2113 achieved the study's primary efficacy endpoint, with a statistically significant greater proportion of patients who received JNJ-2113 achieving PASI-75 responses compared to placebo at Week 16 in all five of the study's treatment groups. A clear dose response was observed across an eight-fold dose range. Treatment was well tolerated, with no meaningful difference in frequency of adverse events across treatment groups versus placebo. It is our expectation that JNJ-2113 will progress into a Phase 3 registrational study in plaque psoriasis on the strength of the FRONTIER1 data. Advancement of JNJ-2113 into a Phase 3 study and meeting the primary endpoint in that study would qualify us for milestone payments of $50 million and $115 million, respectively. Data will be presented from various pre-clinical and clinical studies on JNJ-2113 at medical conferences beginning in the second quarter of 2023.

Other Phase 2 studies of JNJ-2113 that Janssen has initiated include the SUMMIT study of JNJ-2113 for the treatment of moderate-to-severe plaque psoriasis expected to be completed in the second quarter of 2023 and FRONTIER2, a long-term extension study. A Phase 1 trial of an immediate release formulation of JNJ-2113 in healthy Japanese and Chinese adult participants is currently recruiting. Following the completion of Phase 2 studies of JNJ-2113 in plaque psoriasis, we expect Janssen to initiate a separate Phase 2 trial of JNJ-2113 in a second indication. Additional indications may include any or all of psoriatic arthritis, UC and CD.

During the fourth quarter of 2021, we received a $7.5 million milestone payment from Janssen triggered by the completion of data collection for JNJ-2113 Phase 1 activities. In the second quarter of 2022, we received a $25.0 million milestone payment in connection with the dosing of a third patient in FRONTIER1 during the first quarter of 2022. We will be eligible to receive a $10.0 million milestone payment in connection with the dosing of a third patient in the second Phase 2 trial of a second-generation candidate, a $50 million milestone payment upon dosing of a third patient in a Phase 3 trial for a second-generation compound for any indication, and a $115.0 million milestone payment upon a Phase 3 clinical trial for a second-generation compound for any indication meeting its primary clinical endpoint. We

remain eligible for up to approximately $855.0 million in future development and sales milestone payments, in addition to the $112.5 million in nonrefundable payments from Janssen received to date. We also remain eligible to receive tiered royalties on net product sales at percentages ranging from mid-single digits to ten percent.

PN-943

PN-943 is a wholly owned, investigational, orally delivered, gut-restricted alpha 4 beta 7 ("α4β7") specific integrin antagonist for IBD. During the second quarter of 2020, we initiated IDEAL, a 159 patient Phase 2 trial evaluating the safety, tolerability and efficacy of PN-943 in patients with moderate to severe UC. Enrollment in IDEAL was completed during the first quarter of 2022. The trial includes a 12-week induction period, which has been completed, and a 40-week extended treatment period. With the exception of completing the 40-week extended treatment period for eligible patients in the IDEAL trial, which is expected to be completed in the first quarter of 2023, we do not intend to dedicate further internal resources to clinical development or contract manufacturing activities for our PN-943 clinical program.

Discovery Platform

Our clinical assets are all derived from our proprietary discovery platform. Our platform enables us to engineer novel, structurally constrained peptides that are designed to retain key advantages of both orally delivered small molecules and injectable antibody drugs in an effort to overcome many of their limitations as therapeutic agents. Importantly, constrained peptides can be designed to potentially alleviate the fundamental instability inherent in traditional peptides to allow different delivery forms, such as oral, subcutaneous, intravenous, and rectal. We continue to use our peptide technology platform to discover product candidates against targets in disease areas with significant unmet medical needs. For example, we have a pre-clinical stage program to identify an orally active hepcidin mimetic, which we believe will be complementary to the injectable rusfertide for offering the best treatment options for PV, hereditary hemochromatosis and other potential erythropoietic and iron imbalance disorders.

RUSFERTIDE: AN INJECTABLE HEPCIDIN MIMETIC

Rusfertide, an injectable hepcidin mimetic, was discovered through our peptide technology platform. Hepcidin is a natural hormone that regulates iron metabolism. We are developing rusfertide for the treatment of certain disorders characterized by excessive red blood cells ("RBCs"), iron overload or imbalance. In healthy individuals, hepcidin regulates iron levels by limiting release of iron from macrophages and inhibiting iron absorption from the GI tract. In diseases of excessive RBCs, such as PV, the body consumes iron in the production of cells, leading to iron deficiency, which can be exacerbated by phlebotomy. In diseases of iron overload, such as hereditary hemochromatosis, there may be insufficient hepcidin to maintain appropriate iron levels. In other disorders, iron imbalance can benefit from increased levels of hepcidin-like activity to restore proper balance. Native hepcidin is not a practical therapeutic approach because of stability issues, complexity of synthesis and solubility limitations. We developed rusfertide as a more potent, stable, and soluble injectable hepcidin mimetic.

Mechanism of Action and Rationale

The molecular target of the hormone hepcidin is the cellular trans-membrane protein ferroportin, which functions as the major export channel for intracellular iron in splenic macrophages, liver Kupffer cells, hepatocytes, and duodenal enterocytes. Hepcidin binds to the extracellular domain of ferroportin to block the export of iron from inside these cells to the systemic circulation. As a hepcidin mimetic, rusfertide also downregulates ferroportin to control the supply of iron to the bone marrow, thereby normalizing RBC production. In addition, by limiting excessive absorption of dietary iron by enterocytes and rapid sequestration of iron into the macrophages, vital organs can be protected from the accumulation of toxic iron.

Polycythemia Vera ("PV")

PV Overview and Market Opportunity

PV is a rare myeloproliferative neoplasm characterized primarily by the overproduction of RBCs. PV is typically caused by a form of Janus Kinase ("JAK") 2 mutation. PV is a serious chronic condition as the increased RBC count causes the blood to thicken from increased number of smaller rigid RBCs, putting patients at higher risk of cardiovascular and thrombotic events such as heart attack and stroke. According to National Comprehensive Cancer Network ("NCCN") guidelines, age and thrombosis history determine a patient's risk classification as either low-risk or high-risk. Regardless of risk categorization, treatment guidelines for PV are consistent: to control the patient's hematocrit (RBCs as a percentage of whole blood) below 45% in order to reduce the risk of cardiovascular or thrombotic events. PV may progress to myelofibrosis or leukemia.

Currently earlier stage patients are typically treated with low dose aspirin and therapeutic phlebotomy alone or hydroxyurea alone or in combination with phlebotomy. At later stages, patients may receive interferons, marketed as Besrami® or Pegasus®, or JAK inhibitor ruxolitinib, marketed as Jakafi®. Cytoreductive therapies such as hydroxyurea, interferons and ruxolitinib can have challenging side effect profiles as they reduce all cell types, not just RBCs. Current treatments are effective in some patients but have distinct limitations, such as cytopenia and cancer. We believe there are substantial PV patient groups that could benefit from a new non-cytoreductive therapeutic option which focuses on RBCs. NCCN guidelines state that hematocrit levels should be maintained below 45% to reduce risk of cardiovascular and thrombotic events. However, analysis of a large medical claims database indicated that 78% of patients were uncontrolled, with hematocrit test results above 45%. This analysis reveals that current therapies do not offer adequate hematocrit control, indicating a significant unmet need in the United States alone where patients may have an elevated risk of cardiovascular and thrombotic events.

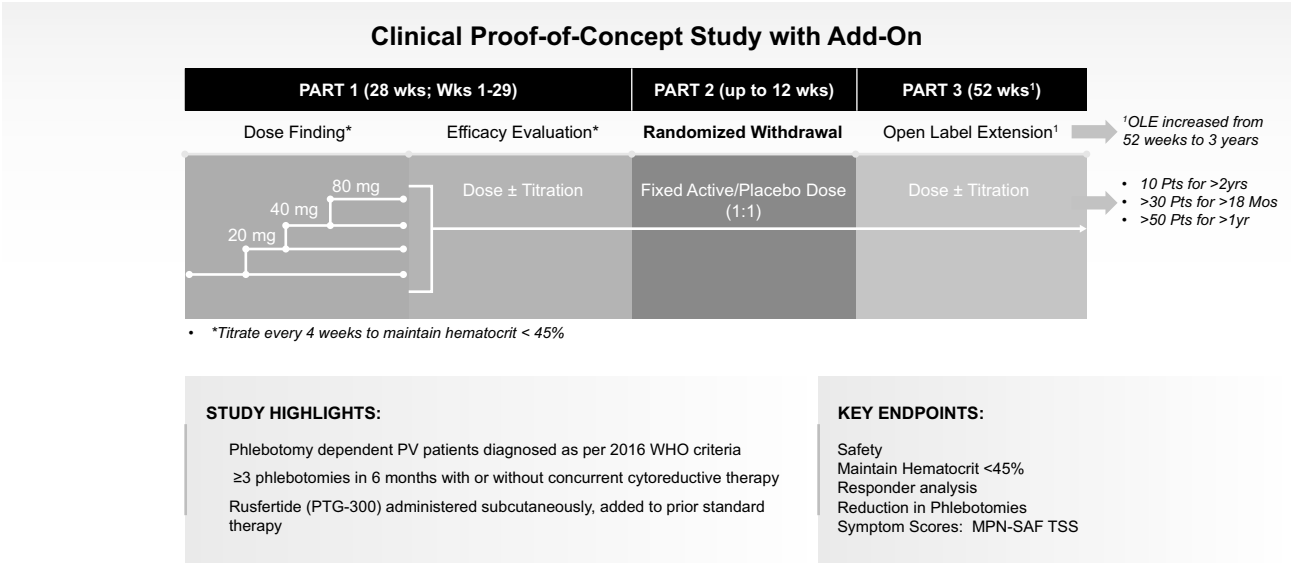
There are approximately 100,000 diagnosed and treated patients living in the United States, with a similar number in Europe, representing an estimated market opportunity of approximately $1.0 billion to $2.0 billion. Patients are typically diagnosed between the ages of 50 and 70 and median survival is approximately 20 years. Analysis of a large medical claims database indicates that the predominant treatment for PV is phlebotomy. Cytoreductive agents, such as hydroxyurea, are also commonly used to control blood count in PV patients. Approximately 60% of PV patients are considered to have moderate treatment burden with treatments including frequent phlebotomy and hydroxyurea. We believe rusfertide can potentially benefit a broad spectrum of patients both as a monotherapy or in combination across the continuum of care.

We believe that rusfertide has the potential to provide substantial benefit to patients by offering a treatment focused on managing hematocrit in a consistent and predictable manner, dramatically decreasing the need for phlebotomy. Rusfertide is a non-cytoreductive mimetic of the natural hormone hepcidin, the master regulator of iron homeostasis in the body. Since high RBC production consumes iron stores, PV can cause iron deficiency, which is often exacerbated by phlebotomy. Rusfertide has a unique iron regulatory mechanism, which data from our Phase 2 REVIVE study suggests allows for persistent control of hematocrit without causing iron deficiency. Rusfertide acts by redistributing iron away from the bone marrow, where iron is essential for RBC production, thereby limiting excess RBC production while still providing sufficient iron levels to support other normal cellular and organ functions.

Clinical Development of Rusfertide in PV

In the fourth quarter of 2019, we initiated REVIVE, a Phase 2 study of rusfertide in PV designed to evaluate safety and preliminary efficacy in patients requiring phlebotomy (Figure 2). The REVIVE study was expected to enroll approximately 60 patients and consisted of a 16-week open-label dose finding stage every 4 weeks from 10 mg to 80 mg and a 12-week maintenance period at doses which generate desired hematocrit levels, followed by a 12-week randomized and blinded withdrawal stage. The study has an open-label extension for up to three years to monitor long term safety and benefits of the drug. The endpoints of this clinical POC study include measurement of blood parameters (hematocrit and hemoglobin levels), reductions or delay in phlebotomy requirements, and improvements in quality-of-life symptoms.

Figure 2. REVIVE: Rusfertide Phase 2 PV Study Design



During the first quarter of 2021, we initiated PACIFIC, a Phase 2 study for rusfertide in up to 20 patients diagnosed with PV and with routinely elevated hematocrit levels (>48%). Rusfertide dosed twice a week was able to reduce patient mean hematocrit from 53% to below 45% in less than 8 weeks for most patients and within 4-6 weeks for a few patients. Once the patient's hematocrit was below 45%, dosing was adjusted and weekly dosing was maintained to control hematocrit without phlebotomy.

We currently have the following designations for rusfertide in PV:

- The FDA granted orphan drug designation for rusfertide for the treatment of PV in June 2020;
- The EMA granted orphan drug designation for rusfertide for the treatment of PV in October 2020; and
- The FDA granted Fast Track designation for rusfertide for the treatment of PV in December 2020.

In consultation with the FDA, we implemented new safety monitoring procedures, including cancer surveillance measures (augmented dermatological examinations) and new stopping rules following a prior 21-day clinical hold on the rusfertide clinical development program. Following the brief clinical hold, over 92% of patients in the REVIVE trial provided reconsent and returned to rusfertide treatment after dosing interruption and re-initiation.

We enrolled 63 patients in the ongoing REVIVE Phase 2 clinical trial of rusfertide in PV prior to the clinical hold and we enrolled seven additional patients to target approximately 50 patients to complete the randomized withdrawal part of the study. The vast majority of patients treated with rusfertide were able to eliminate therapeutic phlebotomies and maintain a target hematocrit level of less than 45 percent. Treatment with rusfertide was also shown to reverse iron deficiency, an important side effect of regular therapeutic phlebotomies as a treatment for PV. Early observations suggest a decreased symptom burden over time, including overall burden (myeloproliferative neoplasm total symptom score), as well as measurements specific to mental function, fatigue and itching.

Preliminary results indicated that rusfertide therapy resulted in rapid, sustained and durable hematocrit control without clinically meaningful changes in white blood cell and platelet counts. Subjects have been under treatment for a median of 1.5 years with the majority of subjects remaining essentially phlebotomy-free. Rusfertide demonstrated similar efficacy in all categories of patients, independent of the PV patient risk category or concurrent therapy with hydroxyurea, interferon or ruxolitinib. Study participation was halted in one patient due to asymptomatic thrombocytosis. One patient developed acute myelogenous leukemia ("AML"), which was deemed not to be related to

rusfertide. Significant adverse events included syncope, peripheral artery aneurysm, gastroenteritis, chest pain, AML, squamous cell carcinoma (skin), melanoma & basal cell carcinoma. Injection site reaction ("ISRs") were most common and associated with 28.1% of injections and are transient in nature.

At the June 2022 ASCO Annual Meeting, we presented updated interim results for REVIVE and PACIFIC demonstrating the effects of dosing interruption and resumption. Rusfertide dosing interruption led to loss of effect, including increased phlebotomy rate and increases in hematocrit and red blood cells. Rusfertide restart restored therapeutic benefits. Following the brief clinical hold described above, over 90% of patients in the REVIVE trial provided reconsent and returned to rusfertide treatment after dosing interruption and reinitiation. At the June 2022 European Hematology Association Congress, we presented interim data as of May 2022 showing that rusfertide treatment interruption reverses hematologic gains and re-initiation of treatment restores therapeutic benefits in patients with PV. At the December 2022 ASH meeting, we presented data as of October 2022 related to rusfertide, including a subgroup of analyses of the adverse event profile from the REVIVE trial. These preliminary results indicated that 84% of treatment-emergent adverse events ("TEAEs") were Grade 2 or below. 16% of patients experienced Grade 3 TEAEs and there were no Grade 4 TEAEs.

On March 15, 2023, we announced positive topline results from the blinded, placebo-controlled, randomized withdrawal portion of the REVIVE trial. Subjects receiving rusfertide achieved statistically significant improvements versus placebo in the trial's primary endpoint.

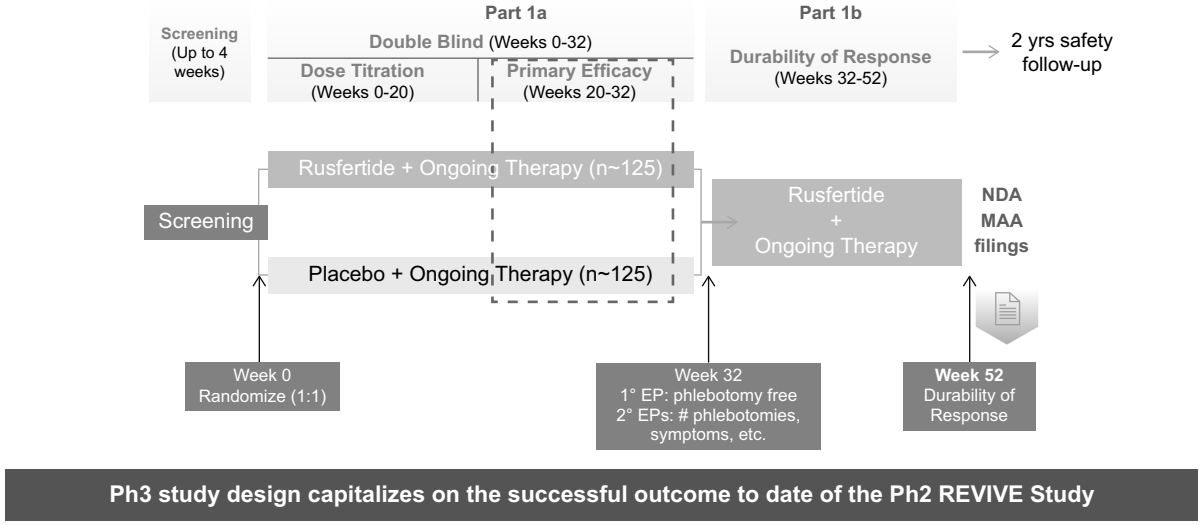
The double-blind, placebo-controlled, 12-week randomized withdrawal portion was included as Part 2 of the REVIVE trial study to evaluate rusfertide in PV patients with frequent phlebotomy requirements. In the REVIVE trial, subjects were initially enrolled in the 28-week open label dose-titration and efficacy evaluation Part 1 of the study, followed by 1:1 randomization of 53 subjects to placebo versus rusfertide therapy for a subsequent duration of 12 weeks. More subjects receiving rusfertide during the blinded randomized withdrawal portion of the REVIVE trial were responders compared with placebo (69.2% versus 18.5%, p=0.0003). A study subject was defined as a responder if the subject completed 12 weeks of double-blind treatment while maintaining hematocrit control without phlebotomy eligibility and without phlebotomy. During the 12 weeks of the blinded randomized withdrawal, only 2 of 26 subjects on rusfertide were phlebotomized.

In addition, in subjects with moderate or severe Myeloproliferative Neoplasm-Symptom Assessment Form (MPN-SAF) symptom scores at baseline, the change from baseline was statistically significant in fatigue, problems with concentration, inactivity and itching during the 28-week open label Part 1 of the trial. Meaningful comparison of symptoms assessments in Part 2 are not possible since a majority of subjects randomized to placebo discontinued prior to the 12-week assessment of MPN-SAF symptoms.

Rusfertide continued to be generally well tolerated in the REVIVE trial, with localized injection site reactions comprising the majority of reported adverse events. No new safety signals were observed in safety data disclosed in connection with the Part 2 efficacy results, relative to the safety data from the REVIVE trial presented at the December 2022 ASH Annual Meeting.

Based on end of Phase 2 feedback provided by the FDA's Division of Nonmalignant Hematology and written comments from the EMA, we activated sites and initiated patient screening for VERIFY, a global Phase 3 clinical trial of rusfertide in PV for approximately 250 patients, in the first quarter of 2022 (Figure 3). Significant efforts have been taken toward the goal of full enrollment and a high degree of interest has been observed from physicians and patient communities. We expect enrollment completion in the fourth quarter of of 2023.

Figure 3. VERIFY: Rusfertide Phase 3 PV Study Design



In consultation with the U.S. Food and Drug Administration, Protagonist has implemented a set of safety monitoring procedures in all ongoing clinical studies, including cancer surveillance measures (dermatological examinations) and stopping rules.

OVERVIEW OF DISEASES DRIVEN BY THE IL-23 PATHWAY: PSORIASIS AND INFLAMMATORY BOWEL DISEASE

IL-23 is a member of the IL-12 family of cytokines with pro-inflammatory and immune stimulatory properties. Cytokines are cell signaling proteins that are released by cells and affect the behavior of other cells. Binding of the IL-23 ligand to the IL-23R receptor leads to an expression of pro-inflammatory cytokines involved in the local tissue autocrine cascade that is an important pathway of many inflammatory diseases, including psoriasis and IBD. The injectable antibody drug Stelara® (marketed for psoriasis, psoriatic arthritis, UC and CD) is a p40 antagonist antibody that inhibits both the IL-23 and IL-12 pathways. Next-generation antibody drugs, such as Tremfya® and Skyrizi®, target the p19 subunit of the IL-23 ligand and are specific inhibitors of the IL-23 pathway, which is believed to be the critical driver of local tissue pathology. Tremfya® and Skyrizi® are approved in psoriasis and psoriatic arthritis ("PsA") and are in Phase 3 clinical trials in UC and CD. Eli Lilly and Company's anti-IL-23 antibody mirikizumab has reported positive results from a Phase 3 program in UC.

Psoriasis

Psoriasis is a chronic inflammatory disease of the skin that affects 130 million people worldwide and 8 million in the United States, translating to 2-3% of the adult population. Psoriasis is associated with several comorbid conditions including cardiovascular disease, obesity, and 30% of psoriasis patients develop arthritic complications. Psoriasis is also associated with significantly decreased quality of life for patients.

Plaque psoriasis is the most common form of psoriasis, which is recognized as the most prevalent immune-mediated inflammatory disease, involving skin and joints and associated with abnormalities of other systems. Several factors, such as surface area covered and symptom burden, impact whether one's psoriasis is considered mild, moderate, or severe. Typically, 3-10% of affected body surface area is considered moderate psoriasis, and more than 10% is considered severe psoriasis. Global market sales for psoriasis therapies in 2020 was $13.2 billion, with U.S. market sales of $10.8 billion. The global market forecast for 2030 anticipates $25.3 billion, with U.S. market sales of $20.9 billion. Identification of the IL-23/IL-17 axis as the key pathway driving psoriatic inflammation has led to the development of more effective and safer systemic therapies that inhibit IL-17 (e.g., Taltz®, Cosentyx®) and IL-23 (e.g., Tremfya®,

Skyrizi®). These biologics have revolutionized the treatment of moderate to severe psoriasis, with superior efficacy and safety compared to conventional oral therapies (e.g., methotrexate, cyclosporin), and first-generation biologics (e.g., anti-TNFs, Stelara®). The anti-IL-17 and anti-IL-23 classes are associated with Psoriasis Area Skin Index ("PASI") 75 scores (75% improvement in skin inflammation) in 90% of patients, and complete clearance of the skin (PASI 100) in 30-40% of patients. The anti-IL-17 class is ineffective in IBD, surprisingly showing overall worsening of disease in Phase 2 studies and is reflected in the product labels. There is still unmet need for new therapies. Only 25% of biologic eligible moderate to severe psoriasis patients are treated with a biologic. The parenteral route of administration for these advanced biologics poses a patient level barrier to entry. Two oral medicines have been approved in moderate to severe psoriasis. Otezla® was approved in 2014. It is the least effective of all drugs approved since 2004 with PASI 75 of approximately 30% but is used widely because of a perceived positive safety profile. In 2022, the first TYK2 inhibitor, Sotyktu®, was approved. In Phase 3 studies, it has demonstrated approximately 55% PASI 75 scores. There is still significant need for safe and effective oral therapies in moderate to severe psoriasis.

Psoriatic Arthritis ("PsA")

PsA is an inflammatory disease of the peripheral and axial joints that complicates psoriasis in up to 30% of patients. Among the 8 million patients in the United States with psoriasis in 2022, it is estimated that approximately 1 million patients have PsA. Many patients with active PsA may have mild psoriasis and many patients with severe psoriasis may have only mild PsA symptoms. PsA is associated with several chronic conditions. PsA may present even before skin symptoms in 10% to 15% of patients. Cardiovascular comorbidities have a higher prevalence in PsA than psoriasis and can impact lifespan and quality of life. Several new targeted therapies have been approved for use in PsA, with additional therapies in development. These advances have improved outcomes, including reductions in musculoskeletal symptoms, skin manifestations and radiographic joint damage. The same drugs approved in psoriasis are also approved in PsA. One notable exception is that the JAK inhibitors, Xeljanz® and Rinvoq®, are approved in PsA without the respective label in psoriasis.

Inflammatory Bowel Disease ("IBD")

IBD is a group of chronic autoimmune and inflammatory conditions of the colon and small intestine, consisting primarily of UC and CD. In UC, inflammation may be limited to part of the colon or extend through its entirety. UC is primarily characterized by ulceration of the intestinal surface, accompanied by rectal bleeding and frequent, urgent bowel movements. CD occurs anywhere along the GI tract, commonly affecting the small intestine and the proximal large intestine. CD complications may include strictures and fistula, which penetrate all layers of the intestine. UC is usually diagnosed earlier than CD due to bleeding symptoms. Patients with CD may initially present with abdominal pain, fatigue and anorexia, which can be misdiagnosed. Both diseases' peak diagnosis years are in young adulthood and are found about equally in both males and females. Management is lifelong and affects school attendance, graduation rates, childbearing and work productivity. IBD prevalence is increasing worldwide and is correlated with the adoption of western diets and lifestyle, as well as genetic factors (5 to 20% of affected patients have a first degree relative with the disease).

According to the Crohn's & Colitis Foundation of America, there are more than 1.6 million IBD patients in the United States alone, an increase of approximately 200,000 patients since 2011. As many as 70,000 new cases of IBD are diagnosed in the United States each year, and there may be as many as 80,000 children in the United States with IBD. In 2020, GlobalData estimated that the UC market was approximately $6.8 billion across eight major markets: United States, Canada, France, Germany, Italy, Spain, United Kingdom and Japan. This is expected to increase at a compound annual growth rate of approximately 6.0% to $12.3 billion by 2029. In 2020, GlobalData estimated that the CD market reached approximately $7.4 billion across those same eight major markets and is expected to grow approximately 5.5% per year to $12.6 billion by 2029.

For many years, tumor necrosis factor-alpha ("TNF-α") antibody drugs were the primary treatment for moderate-to-severe IBD. Humira® and Remicade® are injectable and infused, respectively. Approximately one third of IBD patients do not respond to TNF-α antibody drugs and approximately another 30% to 40% become refractory within the first year of treatment. Additionally, TNF-α antibody drugs may predispose patients to an increased risk of serious

infection and the development of anti-drug antibodies, which over time can cause loss of drug response. More recently, antibody products focused on potentially safer mechanisms of action have been gaining market share. One such product is Takeda Pharmaceuticals' Entyvio®, which targets the α4β7 integrin pathway. Takada Pharmaceuticals reported 2021 sales of Entyvio® of approximately $5.0 billion. Similarly, Johnson & Johnson's Stelara®, which targets the Interleukin 12 ("IL-12") and Interleukin 23 ("IL-23") pathways, has gained significant traction. Johnson & Johnson global sales of Stelara® (approved for psoriasis, psoriatic arthritis, moderate-to-severe CD and UC) exceeded $9.2 billion in 2021. Three anti-IL-23 mAbs are in Phase 3 studies or beyond in IBD: Tremfya®, Skyrizi® and Ely Lilly and Company's mirikizumab. The development of oral medicine has been an unmet need and priority in IBD. The pan-JAK inhibitor Xeljanz® was approved in UC but not CD in 2018. The label contains black box warnings for "an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death". The more selective JAK1/3 inhibitor Rinvoq® was approved in 2022 for UC and CD. The label carries the same black box warnings. The S1P1 modulator class of oral small molecules has also demonstrated efficacy in IBD, with Zeposia® approved in UC (but not CD) in 2021, and etrasimod completing a successful Phase 3 program in UC. The S1P1 class is associated with immunosuppression, cardiac, pulmonary and ocular toxicities.

The development of new, potent and targeted orally delivered therapies for IBD may offer safer and more effective treatment options, alone or in combination, for moderate-to-severe IBD patients. In addition, many clinicians continue to advocate for earlier introduction of targeted therapeutics in mild-to-moderate IBD to prevent disease progression and irreversible gastrointestinal damage. Given that the most effective agents in IBD induce remission in no more than 30% of patients, there has been much recent interest in combination therapies to break through this "therapeutic ceiling". In 2022, Janssen reported results of the VEGA study, the first randomized double bind clinical trial to assess the combination of an anti-TNF (Simponi®) with and anti-IL-23 (Tremfya®) in moderate to severe UC. In the Phase 2a proof-of-concept trial, investigators found 83.1% of patients in the treatment group achieved a clinical response and 36.6% of patients treated with the combination therapy achieved clinical remission. The high rates of clinical response and remission are both higher than the response and remission rates of patients treated with guselkumab alone (74.6%; 21.1%) and golimumab alone (61.1%; 22.2%). Hence, the IL-23 inhibition mechanism is a potentially paradigm shifting combination strategy to improve remission rates in UC.

JNJ-2113: AN ORALLY DELIVERED IL-23R ANTAGONIST

Janssen License and Collaboration Agreement

We have a worldwide license and collaboration agreement with Janssen to research, develop and co-detail our IL-23 receptor ("IL-23R") antagonist compounds for all indications, including IBD. The agreement with Janssen was amended in May 2019 to expand the collaboration by supporting efforts towards second-generation IL-23R antagonists; and in July 2021 to, among other things, enable Janssen to independently research and develop collaboration compounds for multiple indications in the IL-23 pathway and further align our financial interests. See Part II, "Item 7. Management's Discussion and Analysis—Overview" and Note 3 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information. Janssen is an experienced innovator in therapeutics targeting the IL-23 pathway. Stelara® is a monoclonal antibody targeting IL-12 and IL-23 through their common p40 subunit is approved in psoriasis, psoriatic arthritis, CD and UC. Stelara® generated $9.1 billion in sales in 2021. Tremfya® is a specific IL-23 monoclonal antibody. It is approved in psoriasis and psoriatic arthritis, with Phase 3 study results in CD and UC expected in 2023. Tremfya® generated $2.1 billion in sales in 2021. In both psoriasis and IBD, there is an urgent need for safe and effective oral therapies. It is notable that Stelara® loses patent exclusivity in 2023 with biosimilar competition expected.

JNJ-2113 (formerly known as PN-235), an orally delivered IL-23R specific antagonist for the potential treatment of psoriasis, psoriatic arthritis and IBD indications, was discovered through our peptide technology platform. IL-23, a member of the IL-12 family of pro-inflammatory cytokines, is a protein that regulates inflammatory and immune function and plays a key role in the development of IBD. By blocking IL-23R, we believe JNJ-2113 may improve disease symptoms while potentially minimizing the risk of systemic side effects. During the fourth quarter of 2021, a portfolio decision was made by Janssen to advance development of our IL-R antagonist JNJ-2113. For JNJ-2113,

Janssen is primarily responsible for the conduct of all further development, and we were primarily responsible for the discovery, IND-enabling studies and the initial Phase 1 study.

Clinical Development of JNJ-2113

A Phase 1 study was initiated for JNJ-2113 in December 2020. The Phase 1 study for JNJ-2113 was designed to determine the safety, tolerability and pharmacokinetics of JNJ-2113 in 107 healthy volunteers. The study was conducted in three parts: a SAD component, a MAD component, and a randomized, crossover solid dose comparison component. The primary endpoint was safety as measured by number and severity of adverse events. Secondary outcomes included pharmacokinetics measurements of peak concentration and area under the curve. The Phase 1 study was completed in September 2021. Results of the Phase 1 study demonstrated that administration of JNJ-2113 was well-tolerated. No serious adverse events or dose-limiting toxicities were observed. The pharmacokinetic and pharmacodynamic parameters of JNJ-2113 were consistent with those predicted by pre-clinical studies.

FRONTIER1, a Phase 2b study in moderate-to-severe plaque psoriasis, was initiated by Janssen in February 2022 and was completed in December 2022. In February 2022, Janssen initiated FRONTIER1, a 255-patient Phase 2b clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis, which was completed in December 2022. FRONTIER1 was a randomized, multicenter, double-blind, placebo-controlled study that evaluated three once-daily dosages and two twice-daily dosages of JNJ-2113 taken orally. The primary endpoint of the study is the proportion of patients achieving PASI-75 (a 75% improvement in skin lesions as measured by the Psoriasis Area and Severity Index) at 16 weeks. In March 2023, we announced positive topline results from the trial. JNJ-2113 achieved the study's primary efficacy endpoint, with a statistically significant greater proportion of patients who received JNJ-2113 achieving PASI-75 responses compared to placebo at Week 16 in all five of the study's treatment groups. A clear dose response was observed across an eight-fold dose range. Treatment was well tolerated, with no meaningful difference in frequency of adverse events across treatment groups versus placebo. It is our expectation that JNJ-2113 will progress into a Phase 3 registrational study in plaque psoriasis on the strength of the FRONTIER1 data. Advancement of JNJ-2113 into a Phase 3 study and meeting the primary endpoint in that study would qualify us for milestone payments of $50 million and $115 million, respectively. Data will be presented from various pre-clinical and clinical studies on JNJ-2113 at medical conferences beginning in the second quarter of 2023.

Other studies of JNJ-2113 that Janssen has initiated include the SUMMIT study of JNJ-2113 for the treatment of moderate-to-severe plaque psoriasis expected to be completed in the second quarter of 2023, and FRONTIER2, a long-term extension study. A Phase 1 trial of an immediate release formulation of JNJ-2113 in healthy Japanese and Chinese adult participants is currently recruiting. Following the completion of Phase 2 studies of JNJ-2113 in plaque psoriasis, we expect Janssen to initiate a separate Phase 2 trial of JNJ-2113 in a second indication.

OUR PEPTIDE TECHNOLOGY PLATFORM

Our proprietary technology platform is purposefully built to exploit the advantages of constrained peptides, which are much smaller than antibody-based drugs and may be delivered orally but are big enough to bind and block the difficult targets that antibodies bind and modulate. The platform has been successfully applied to a diverse set of biological targets that has led to several pre-clinical and clinical stage peptide-based new chemical entities, including our clinical stage product candidates, for a variety of clinical indications. Our platform is comprised of a series of tools and methods, including a combination of molecular design, phage display, stability assays, medicinal chemistry, surrogate biomarkers, formulations, *in vitro* biochemical, cell and tissue-based assays, and *in vivo* pharmacology and pharmacokinetic approaches. We apply this platform to the discovery and development of constrained peptides as new drug candidates.

The platform is used to develop potential drug candidates (agonists and antagonists): (i) using the structure of a target, when available, (ii) *de novo* when no target structure exists, or (iii) from publicly disclosed peptide starting points. In a structure-based approach, our proprietary molecular design software and structural database of several thousand constrained peptides, termed Vectrix™, are screened to identify suitable scaffolds. The scaffolds identified form the basis of designing and constructing the first set of phage or chemical libraries. The initial hits are identified by

either panning or screening such libraries, respectively. When structural information is unavailable for a target, hits are identified by panning a set of 34 proprietary cluster-based phage libraries consisting of millions of constrained peptides. Once the hits are identified, they are optimized using a set of peptide, peptide mimetic and medicinal chemistry techniques that include the incorporation of new or manipulation of existing cyclization-constraints, as well as natural or unnatural amino acids and chemical conjugation or acylation techniques. These techniques are applied to optimize potency, selectivity, stability, exposure and ultimately efficacy. For rusfertide, hit discovery and optimization relied exclusively on medicinal and computational chemistry, with no phage display, to develop potent and selective injectable candidates with enhanced stability and exposure in blood. For injectable products, stability in blood is determined using *in vitro* assay techniques to identify chemical and biological sites of degradation, which are then optimized while still maintaining potency and selectivity. Conjugation strategies are used to optimize the exposure of the injected peptide. For JNJ-2113, phage display is tightly coupled to medicinal chemistry, structural biology and oral stability techniques to develop potent, selective and orally delivered molecules. Oral stability is profiled in a series of *in vitro* and *ex vivo* assays that portray the chemical and metabolic barriers a peptide will encounter as it transits the GI and systemic compartments as needed. These metabolically labile spots in the peptides are optimized using medicinal chemistry-based approaches to engineer oral stability while maintaining selectivity and potency. Various *in vivo* pharmacology tools are then used to quantify peptide exposure in relevant GI and systemic compartments as needed organs and tissues. This data can be used to optimize required exposure over the required time frame to achieve *in vivo* efficacy. This is complemented by formulation technologies to enhance GI and systemic exposure by exploiting the intrinsic stability of our oral peptides. Finally, various biomarkers are also developed to correlate exposure with efficacy to guide candidate selection, dose selection and provide preliminary proof-of-concept of target engagement in clinical trials.

Discovery and Preclinical Activities

We believe we have built a versatile, well-validated and unique discovery platform. For example, this peptide technology platform has been used to develop product candidates for diverse target classes including G-protein-coupled receptors, ion channels, transporters, cytokines and their receptors for a variety of therapeutic areas. In the future we may tackle other GI and blood disorders and expand our technology platform to provide potential opportunities to pursue a wider variety of diseases that may include topical and systemic approaches. As an example, the gut may communicate with the immune, central nervous, and endocrine systems, providing the potential of our GI-restricted approach to treat systemic autoimmune, metabolic, cancer and cardiovascular diseases. We also intend to progress our platform to achieve systemic bioavailability and activity with oral peptides, macrocycles and peptidomimetics, thereby enabling us to address systemic diseases. Examples of this approach are our pre-clinical stage program to identify an orally active hepcidin mimetic, as was reported at the American Society for Hematology's virtual annual meeting in December 2020, and the discovery and development of JNJ-2113, our IL-23R antagonist in collaboration with Janssen. We believe the oral hepcidin mimetic will be complementary to the injectable rusfertide for offering the best treatment options for PV, hereditary hemochromatosis and other potential erythropoietic and iron imbalance disorders.

Competition

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. While we believe that our product candidates, technology, knowledge and experience provide us with certain competitive advantages, we face competition from established and emerging pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions, among others.

Rusfertide

Ruxolitinib, marketed as Jakafi®, was approved in 2014 for the treatment of adults with PV who have inadequate response to or are intolerant to HU. Approximately 5,300 PV patients are treated with Jakafi® each year. Besremi®, a ropeginterferon alfa-2b product indicated for the treatment of adults with PV, was approved with a black box warning in November 2021.

We are aware of other investigational compounds under clinical development for treatment of PV, including short interfering RNA approaches aimed at modulating or increasing endogenous hepcidin levels.

JNJ-2113

In psoriasis and psoriatic arthritis, competition will come from companies with approved injectable agents in the IL-17 and IL-12/23 pathway including Cosentyx®, Taltz®, Siliq®, Tremfya®, and Skyrizi®. Bimekizumab (anti-IL-17A and F, UCB) has completed a positive Phase 3 program in psoriasis. Otezla® (Amgen) was the first oral agent approved in both psoriasis and PsA. The oral JAK inhibitors Xeljanz® (Pfizer) and Rinvoq® are approved in PsA but not psoriasis. Several oral small molecules that inhibit the Janus kinase Tyk2 are advancing in development. The Bristol Myers Squibb ("BMS") TYK2 inhibitor, Sotyktu®, was approved for psoriasis in 2022. Second generation allosteric TYK2 inhibitors from Nimbus Therapeutics (recently in-licensed by Takeda Pharmaceuticals) are moving into Phase 3 development, and a molecule from Ventyx Biosciences has initiated Phase 2. Several small molecules that inhibit IL-17 have completed Phase 1 clinical development.

In IBD, competition will come from companies with injectable agents in the anti-integrin class (Entyvio®, Takeda®, approved) and the anti-IL-12/23 class that may be approved in the next several years, including Janssen's Stelara® (approved in UC and CD), Abbvie's risankizumab (Skyrizi®) (UC and CD Phase 3), Janssen's guselkumab (Tremfya®) (UC and CD); and Eli Lilly's mirikizumab (UC and CD).

In addition, orally delivered agents with novel mechanisms of action that are approved for or in development and may be approved for UC and/or CD prior to or shortly after the launch of our product candidates can have significant impact in the competitive environment, including,

- JAK inhibitors: The pan-JAK tofacitinib (Xeljanz®) is approved in UC. The next-generation selective JAK1/3 inhibitors, including Abbvie's upadacitinib (Rinvoq®) was approved in UC and CD in 2022. Pfizer's selective JAK1/TEC inhibitor ritlecitinib is in Phase 2 development for UC and CD; and

- S1P1 receptor modulators: Bristol Myers Squibb ozanimod (Zeposia®) is approved in UC. Second-generation agents including Pfizer's etrasimod (Phase 3 UC, Phase 2b CD) are in development.

Morphic Therapeutics is developing MORF-057, an oral small molecule targeting α4β7 entering Phase 2 development in UC. Other oral small molecules targeting α4β7 from Gilead and EA Pharma are in early clinical development. Many other agents are in early-stage development in IBD, including injectable anti-TLIA antibodies by Pfizer and Prometheus, which have both recently presented positive Phase 2 results in UC.

Both the psoriasis and IBD market will be impacted by the launch of biosimilars for Humira® and Stelara® in 2023.

Material Agreements

Janssen License and Collaboration Agreement

On July 27, 2021, we entered into an amended and restated License and Collaboration Agreement (the "Restated Agreement") with Janssen, which amended and restated the License and Collaboration Agreement effective July 13, 2017, by and between us and Janssen (the "Original Agreement"), as amended by the First Amendment thereto, effective May 7, 2019 (the "First Amendment"). Janssen is a related party to us as Johnson & Johnson Innovation—JJDC, Inc., a significant stockholder of ours, and Janssen are both subsidiaries of Johnson & Johnson. Upon the effectiveness of the Original Agreement, we received a non-refundable, upfront cash payment of $50.0 million from Janssen. Upon the effectiveness of the First Amendment in 2019, we received a $25.0 million payment from Janssen in 2019. We received a $5.0 million payment triggered by the successful nomination of a second-generation IL-23R antagonist development compound during the first quarter of 2020, and we received a $7.5 million payment for completion of data collection

activities for the first Phase 1 clinical trial of a second-generation compound during the fourth quarter of 2021. We received a $25.0 million payment during the second quarter of 2022 triggered by the dosing of a third patient in FRONTIER1. See Part II, Item 7. “Management’s Discussion and Analysis—Overview” and Note 3 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Research Collaboration and License Agreement with Zealand Pharma A/S

In June 2012, we entered into a Research Collaboration and License Agreement (the “Zealand Agreement”) with Zealand Pharma A/S (“Zealand”) to identify, optimize and develop novel disulfide-rich peptides to discover a hepcidin mimetic. We amended this agreement on February 28, 2014, at which point Protagonist assumed responsibility for the development program. See Part II, Item 7. “Management’s Discussion and Analysis—Contractual Obligations and Other Commitments” and Note 7 and Note 11 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Intellectual Property

We strive to protect and enhance the proprietary technology, inventions, and improvements that are commercially important to the development of our business, including seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties. We also rely on trade secrets relating to our proprietary technology platform and on know-how, and continuing technological innovation to develop, strengthen, and maintain our proprietary position in the field of peptide-based therapeutics that may be important for the development of our business. We will also take advantage of regulatory protection afforded through data exclusivity, market exclusivity and patent term extensions where available.

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business; defend and enforce our patents; preserve the confidentiality of our trade secrets; and operate without infringing the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same. For more information, please see Item 1A. “Risk Factors—Risks Related to Our Intellectual Property.”

We own or co-own 15 issued U.S. patents, over 60 granted ex-U.S. patents, and numerous U.S. and ex-U.S. patent applications related to our clinical assets. We possess substantial know-how and trade secrets relating to the discovery, development and commercialization of peptide based therapeutic products. Our proprietary intellectual property, including patent and non-patent intellectual property, is generally directed to, for example, peptide-based therapeutic compounds and compositions, methods of using these peptide-based therapeutic compounds and compositions to treat or prevent disease, methods of manufacturing peptide-based therapeutic compounds and compositions, and other proprietary technologies and processes related to our lead product development candidates. Specific patents and patent applications are directed to compositions of α*4*β7 integrin peptides, IL-23R antagonist peptides, and hepcidin and enkephalin mimetics peptides, as well as methods of synthesizing and using these peptides to treat inflammatory disorders. Applications are currently pending in the United States and other major jurisdictions, including Australia, Canada, China, Japan, and Europe. We expect our patents and patent applications, if issued, and if the appropriate maintenance, renewal, annuity, or other governmental fees are paid, to expire from October 2033 to July 2041 (excluding possible patent term extensions).

Our objective is to continue to expand our portfolio of patents and patent applications in order to protect our clinical assets and related peptide-based drug technologies.

We also license patents and patent applications directed to processes and methods related to our technology platform. These patents have issued in the United States and other major jurisdictions, including Australia and Europe. Some licensed patents are expired, and others are expected to expire before or by February 2023. Material aspects of our technology platform are protected by trade secrets and confidentiality agreements.

In addition to the above, we have established expertise and development capabilities focused in the areas of pre-clinical research and development, manufacturing and manufacturing process scale-up, quality control, quality assurance, regulatory affairs and clinical trial design and implementation. We believe that our focus and expertise will help us develop products based on our proprietary intellectual property.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in 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 an FDA approved drug may also be eligible for patent term extension, which permits patent term restoration of a U.S. patent as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Moreover, a patent can only be extended once, and thus, if a single patent is applicable to multiple products, it can only be extended based on one product. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. When possible, we expect to apply for patent term extensions for patents covering our product candidates and their methods of use.

Trade Secrets

We rely on trade secrets to protect certain aspects of our technology, particularly in relation to our technology platform. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors and contractors. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For more information, please see Item 1A. "Risk Factors—Risks Related to Our Intellectual Property."

Manufacturing

We contract with third parties for the manufacturing of our product candidates for pre-clinical and clinical studies and eventually for commercial supplies and intend to continue to do so in the future. We do not own or operate any manufacturing facilities and we have no plans to build any owned clinical or commercial scale manufacturing capabilities. We believe that the use of contract manufacturing organizations ("CMOs") eliminates the need for us to directly invest in manufacturing facilities, equipment and additional staff. We have established a global supply chain for raw material, active pharmaceutical ingredients ("API"), drug product manufacturing and distribution. We work with contract manufacturers in the United States, Europe and Asia. Although we rely on contract manufacturers, our personnel and consultants have extensive manufacturing and quality control experience overseeing CMOs. We regularly consider second source or back-up manufacturers for both API and drug product manufacturing. To date, our third-party manufacturers have met the manufacturing requirements for our product candidates. We expect third-party manufacturers to be capable of providing supplies needed for our product candidates to meet anticipated full-scale

commercial demands, and we have selected CMOs that can manufacture our product candidates for our ongoing and planned clinical trials as well as commercial supplies. We currently engage CMOs on a "fee for services" basis for our current development and clinical supplies.

Government Regulation

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial requirements upon companies involved in the clinical development, manufacture, marketing and distribution of drugs, such as those we are developing. These agencies and other federal, state and local entities regulate, among other things, the research and development, testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion, distribution, post-approval monitoring and reporting, sampling and export and import of our product candidates.

U.S. Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act ("FDCA") and its implementing regulations. The process of obtaining regulatory approvals and the compliance with applicable federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending new drug applications ("NDAs"), withdrawal of an approval, imposition of a clinical hold, issuance of warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of pre-clinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practices regulations;
- submission to the FDA of an IND application, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board ("IRB") at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practice ("GCP") requirements to establish the safety and efficacy of the proposed drug product for each indication;
- submission to the FDA of an NDA (or Biologics License Application ("BLA") for a biologic product);
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with current good manufacturing practices ("cGMP") requirements and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- satisfactory completion of an FDA inspection of one or more clinical trial sites to assure compliance with GCP requirements and the clinical protocol; and

- FDA review and approval of the NDA.

Pre-clinical Studies

Pre-clinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. These pre-clinical studies must comply with good laboratory practices ("GLP"). An IND sponsor must submit the results of the pre-clinical tests, together with manufacturing information, analytical data and any available clinical data or literature to the FDA as part of an IND. Some pre-clinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements. GCP requirements mandate that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under protocols detailing the objectives of the trial, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND (or equivalent international submission). In addition, an IRB or ethics committee ("EC") must review and approve the plan for any clinical trial at all institutions participating in the clinical trial before it commences at that site. Information about certain clinical trials must be submitted within specific time frames to the National Institutes of Health ("NIH") for public dissemination on www.clinicaltrials.gov.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined:

- Phase 1: The drug is initially introduced into healthy human subjects or patients with the target disease or condition and is tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness.

- Phase 2: The drug is administered to a limited patient population to identify possible adverse effects and safety risks, and to preliminarily evaluate the efficacy of the investigational drug product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- Phase 3: The drug is administered to an expanded patient population to establish the overall risk-benefit profile of the product, and to provide adequate labeling information (labeling) for the safe and efficacious administration for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB or EC can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

Marketing Approval

Following successful completion of the required clinical testing, the results of the pre-clinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other information, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to an application user fee. Under the

Prescription Drug User Fee Act ("PDUFA") guidelines, the FDA has a target of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to FDA.

In addition, under the Pediatric Research Equity Act of 2003 ("PREA") certain NDAs or supplements to an NDA must contain data that are adequate to assess the safety and effectiveness of the drug 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. The FDA may, on its own initiative or at the request of the applicant, 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.

The FDA also may require submission of a risk evaluation and mitigation strategy ("REMS") plan to ensure that the benefits of the drug outweigh its risks. REMS plans typically include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the requested information. The resubmitted application is also subject to review before the FDA accepts it for filing. After the submission is accepted for filing, the FDA begins a substantive review. The FDA reviews an NDA to determine whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. 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 carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA may inspect one or more clinical trial sites to assure compliance with GCP requirements.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter or a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or pre-clinical testing for the FDA to reconsider the application. Even after submission of this additional information, the FDA may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product. It may also require that contraindications, warnings or precautions be included in the product labeling or require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval. In addition, the FDA may mandate testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS. This can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of

alterations, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Fast Track Designation

The FDA has various programs, such as fast track designation. These programs are intended to expedite or simplify the process for the development and FDA review of drugs for the treatment of serious or life threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients faster. The sponsor of a new drug may request fast track designation concurrent with, or after, the filing of the IND. To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need. A product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety. Fast track designation provides additional opportunities for interaction with the FDA's review team and may allow for rolling review of NDA components before the completed application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA. However, the FDA's time goal for reviewing an application does not begin until the last section of the NDA is submitted. The FDA may decide to rescind the fast track designation if it determines that the qualifying criteria no longer apply.

Orphan Designation

The FDA may grant orphan designation to drugs or biologics intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States. The FDA may also grant the designation if the disease affects more than 200,000 individuals in the United States, and there is no reasonable expectation that the cost of developing and marketing the product for this type of disease or condition will be recovered from sales in the United States. Orphan designation must be requested before submitting an NDA or BLA. After the FDA grants orphan designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

In the United States, orphan designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan exclusivity, which means the FDA may not approve any other application to market the same product for the same indication for a period of seven years, except in limited circumstances. Such circumstances include a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer with orphan exclusivity is unable to assure sufficient quantities of the approved orphan designated product. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity.

Breakthrough Therapy Designation

A sponsor can request designation of a drug candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated

approval and priority review. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. The FDA may decide to rescind the breakthrough designation if it determines that the qualifying criteria no longer apply.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA. These regulations include requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to FDA review and approval. There also are continuing, annual program user fee requirements for any marketed products.

The FDA may impose a number of post-approval requirements as a condition of approval of an NDA. For example, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies. They are subject to periodic unannounced inspections by the FDA and state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations require investigation and correction of any deviations from cGMP requirements and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

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

- 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 NDAs or supplements to approved NDAs, or suspension or revocation of product 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 marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved prescribing information. The FDA and other agencies enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Coverage and Reimbursement

Sales of our product candidates, if approved, will depend, in part, on the extent to which the cost of such products will be covered and adequately reimbursed by third-party payors, such as government healthcare programs, commercial insurance and managed health care organizations. These third-party payors are increasingly limiting coverage and reducing reimbursements for medical products and services by challenging the prices and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. If these third-party payors do not consider our products to be cost-effective compared to other therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

There is no uniform policy requirement for coverage and reimbursement for drug products among third-party payors in the United States. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Coverage determination can be a time-consuming and costly process that may 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 obtained or applied consistently. Even if reimbursement is provided, market acceptance of our products may be adversely affected if the amount of payment for our products proves to be unprofitable for health care providers or less profitable than alternative treatments, or due to administrative burdens.

In addition, the U.S. government, state legislatures and foreign governments have continued 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 our net revenue and results. Decreases in third-party reimbursement for our product candidates or a decision by a third-party payor to not cover our product candidates could reduce physician usage of our products candidates, once approved, and have a material adverse effect on our sales.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to as the ACA, enacted in March 2010, has had and is expected to continue to have a significant impact on the health care industry. The ACA imposes a significant annual fee on certain companies that manufacture or import branded prescription drug products. The ACA also increased the Medicaid rebate rate and expanded the rebate program to include Medicaid managed care organizations. It also contains substantial new provisions intended to broaden access to health insurance, reduce the growth of health care spending, enhance remedies against health care fraud and abuse, add new transparency requirements for the health care industry, impose new taxes and fees on pharmaceutical manufacturers, and impose additional health policy reforms, any or all of which may affect our business.

There have been executive, judicial and Congressional challenges to certain aspects of the ACA. For example, President Trump signed several Executive Orders and other directives designed to delay the implementation of certain ACA requirements or otherwise circumvent some of the health insurance mandates. Concurrently, Congress considered legislation to repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the ACA have been enacted. The Tax Cuts and Jobs Act of 2017, or the Tax Act, included a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on some individuals who do not maintain qualifying health coverage for all or part of a year. Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated “Cadillac” tax on high-cost employer-sponsored health coverage and the medical device tax, and also eliminated the health insurance tax. The Bipartisan Budget Act of 2018 amends the ACA to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole”, and increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in the Medicare Part D program. The IRA, enacted August 16, 2022, aims to control prescription drug prices in the upcoming years. The IRA will allow the Centers for Medicare & Medicaid Services (“CMS”) to cap out-of-pocket costs in 2025 and to negotiate prescription drug prices in 2026 for the first time. Additionally, the IRA provides a new “inflation rebate” covering Medicare patients to take effect in 2023 to prevent rapid and arbitrary price increases in prescription drugs. These and any other legislation or healthcare reform measures of the Biden administration may impact the ACA and our business. There may also be

further challenges to the ACA, and new laws may also result in additional reductions in Medicare and other health care funding.

Further, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. This scrutiny has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the Trump administration implemented drug pricing reform through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that attempt to implement several of the administration's proposals The FDA also released a final rule, effective November 30, 2020, implementing a portion of the importation executive order providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule was delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers.

Federal and state legislatures have become 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.

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 therapies. Further, it is possible that additional governmental action is taken in response to the COVID-19 pandemic.

It is uncertain whether and how future legislation, whether domestic or foreign, could affect prospects for our product candidates or what actions payors for health care treatment and services may take in response to such health care reform proposals or legislation. Adoption of price controls and other cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures reforms may prevent or limit our ability to generate revenue, attain profitability or commercialize our product candidates.

Other Health Care Laws and Compliance Requirements

We will also be subject to health care regulation and enforcement by the federal and state government and foreign governments in which we will conduct our business once our products are approved. The laws that may affect our ability to operate include the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), as amended by the Health Information Technology for Economic and Clinical Health Act, which governs the conduct of certain electronic health care transactions and protects the security and privacy of protected health information; the criminal health care fraud statutes under HIPAA also prohibits persons and entities from knowingly and willfully executing a scheme to defraud any health care benefit program, including private payors, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for health care benefits, items or services; the Anti-Kickback Statute, which prohibits persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in exchange for or to induce either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal health care programs such as the Medicare and Medicaid programs; federal false claims laws and civil monetary penalties laws that prohibit any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid; and the Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or Children's Health Insurance Program to report annually to the HHS information related to

payments and other transfers of value made to various healthcare professionals including physicians, physician assistants, nurse practitioners and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members.

The majority of states also have statutes or regulations similar to the federal anti-kickback and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. We may be subject to state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. In addition, we may be subject to reporting requirements under state transparency laws, as well as state laws that require pharmaceutical companies to comply with the industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government that otherwise restricts certain payments that may be made to health care providers and entities. In addition, certain states and local jurisdictions require the registration of pharmaceutical sales representatives.

Because of the breadth of these laws and the narrowness of available statutory and regulatory exceptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If we are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including significant administrative, civil and criminal penalties, damages, fines, imprisonment, disgorgement, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, exclusion of products from reimbursement under U.S. federal or state health care programs, and the curtailment or restructuring of our operations.

Government Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing clinical studies and any commercial sales and distribution of our products.

Drug and Biologic Development Process in the European Union ("EU")

All clinical trials included in applications for marketing authorization for human medicines in the EU must be carried out in accordance with EU regulations. This means that such clinical trials must comply with EU clinical trial legislation, as well as ethical principles equivalent to those set out in the EEA, including adhering to international good clinical practice and the Declaration of Helsinki. The conduct of clinical trials in the EU is governed by the EU Clinical Trials Regulation (EU) No. 536/2014 ("CTR") which entered into force on January 31, 2022.

Under the CTR, a sponsor may submit a single application for approval of a clinical trial through a centralized EU clinical trials portal. One national regulatory authority (the reporting EU Member State proposed by the applicant) will take the lead in validating and evaluating the application consult and coordinate with the other concerned Member States. If an application is rejected, it may be amended and resubmitted through the EU clinical trials portal. If an approval is issued, the sponsor may start the clinical trial in all concerned Member States. However, a concerned EU Member State may in limited circumstances declare an "opt-out" from an approval and prevent the clinical trial from being conducted in such Member State. The CTR also aims to streamline and simplify the rules on safety reporting, and introduces enhanced transparency requirements such as mandatory submission of a summary of the clinical trial results to the EU Database.

National laws, regulations, and the applicable GCP and Good Laboratory Practice standards must also be respected during the conduct of the trials, including the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use ("ICH") guidelines on Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki.

Drug Marketing Authorization

In the EU and in Iceland, Norway and Liechtenstein (together, the European Economic Area or "EEA"), after completion of all required clinical testing, pharmaceutical products may only be placed on the market after obtaining a Marketing Authorization ("MA"). To obtain an MA of a drug under EU regulatory systems, an applicant can submit a Marketing Authorization Application ("MAA") through, amongst others, a centralized or decentralized procedure.

The centralized procedure provides for the grant of a single MA that is issued by the European Commission ("EC") following the scientific assessment of the application by the EMA that is valid for all EU Member States as well as in the three additional EEA Member States. The centralized procedure is compulsory for specific medicinal products, including for medicines developed by means of certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products ("ATMP") and medicinal products with a new active substance indicated for the treatment of certain diseases (AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases). For medicinal products containing a new active substance not yet authorized in the EEA before May 20, 2004 and indicated for the treatment of other diseases, medicinal products that constitute significant therapeutic, scientific or technical innovations or for which the grant of a MA through the centralized procedure would be in the interest of public health at EU level, an applicant may voluntarily submit an application for a marketing authorization through the centralized procedure.

Under the centralized procedure, the Committee for Medicinal Products for Human Use ("CHMP"), established at the EMA, is responsible for conducting the initial assessment of a drug. The timeframe for the evaluation of an MAA by the CHMP is, in principle, 210 days from receipt of a valid MAA. However, this timeline excludes clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP, so the overall process typically takes a year or more, unless the application is eligible for an accelerated assessment. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. Upon request, the CHMP can reduce the time frame to 150 days if the applicant provides sufficient justification for an accelerated assessment. The CHMP will provide a positive opinion regarding the application only if it meets certain quality, safety and efficacy requirements. This opinion is then transmitted to the EC, which has the ultimate authority for granting MA within 67 days after receipt of the CHMP opinion.

Medicines that fall outside the mandatory scope of the centralized procedure have three routes to authorization: (i) they can be authorized under the centralized procedure if they concern a significant therapeutic, scientific or technical innovation, or if their authorization would be in the interest of public health; (ii) they can be authorized under a decentralized procedure where an applicant applies for simultaneous authorization in more than one EU Member State; or (iii) they can be authorized in an EU Member State in accordance with that state's national procedures and then be authorized in other EU countries by a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization (mutual recognition procedure).

The decentralized procedure permits companies to file identical MA applications for a medicinal product to the competent authorities in various EU Member States simultaneously if such medicinal product has not received marketing approval in any EU Member State before. The competent authority of a single EU Member State, known as the reference EU Member State, is appointed to review the application and provide an assessment report. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference EU Member State and concerned EU Member States. The reference EU Member State prepares a draft assessment report and drafts of the related materials within 120 days after receipt of a valid application. Subsequently, each concerned EU Member State must decide whether to approve the assessment report and related materials. If an EU Member State cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the EC, whose decision is binding for all EU Member States.

All new MAAs must include a Risk Management Plan ("RMP"), describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product.

RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available. The regulatory authorities may also impose specific obligations as a condition of the MA.

Marketing Authorizations have an initial duration of five years. After these five years, the authorization may subsequently be renewed on the basis of a reevaluation of the risk-benefit balance. Once renewed, the MA is valid for an unlimited period unless the EC or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with only one additional five-year renewal. Applications for renewal must be made to the EMA at least nine months before the five-year period expires.

European Data Protection Laws

The collection and use of personal health data and other personal data in the EU is governed by the provisions of the European General Data Protection Regulation (EU) 2016/679 ("GDPR"). The GDPR imposes strict requirements on the processing of personal data, including the legal basis for the processing, the information that has to be provided to individuals before their data is processed, notification obligations to national data protection authorities, and the technical and organization measures to ensure the security and confidentiality of the personal data. EU Member States may also have additional requirements for health, genetic, and biometric data through their national legislation. The GDPR also imposes restrictions on the transfer of personal data to countries outside of the EU that do not provide an adequate level of data protection. To enable such transfers, appropriate safeguards, such as standard contractual clauses ("SCCs"), must be in place.

Environmental, Social, Governance and Human Capital Disclosures

Governance and Leadership

Our commitment to integrating sustainability across our organization begins with our board of directors, which has oversight of strategy and risk management related to Environmental, Social and Governance ("ESG").

Business Ethics

We are committed to creating an environment where we are able to excel in our business while maintaining the highest standards of business conduct and ethics. Our Code of Business Conduct and Ethics ("Code of Conduct") reflects the business practices and principles of behavior that supports this commitment, including our policies on bribery, corruption, conflicts of interest, insider trading, and our whistleblower program. We expect all of our directors, officers, and employees to read, understand, and comply with the Code of Conduct and its application to the performance of his or her business responsibilities.

Environmental Commitment

We are committed to protecting the environment and attempt to mitigate any negative impact of our operations, promoting reuse and recycling and conserving resources, where feasible. We have safety protocols in place for handling biohazardous waste in our operations, including in our clinical trials, and we use third-party vendors for biohazardous waste and chemical disposal.

Social Responsibility

We are committed to providing patients with access to our investigational therapies, to the extent appropriate at the development stage. We are currently focused on our clinical programs and getting our therapies through the approval process and approved as rapidly as possible provided they are shown to be safe and effective. We provide access to our investigational therapies through our clinical trials, including in some cases long-term extensions of those trials that provide access to our therapies for up to several years. We also support educational efforts related to therapeutic areas in focus for our company, and life sciences education more broadly. In addition to financial support of continuing

education, we are active sponsors, mentors, and hosts for students seeking to broaden their understanding of life sciences in the interest of advancing human health.

Human Capital

As of December 31, 2022, we had 105 full-time equivalent employees, 82 of whom were in research and development, of which 3 hold an M.D. and 24 hold Ph.D. degrees. The remaining 23 employees worked in finance, legal, business development, human resources and administrative support, of which one holds a Ph.D. 97 of our full-time equivalent employees are located in the United States and 8 are located in Australia. None of our employees are represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good. We track and report internally on key talent metrics including workforce demographics, diversity data and the status of open positions. We are committed to equality, inclusion and diversity in the workplace. As of December 31, 2022, nearly 70% of our workforce identify as members of underrepresented ethnic communities and 55% identify as female. We strive to interview diverse candidates for our open positions.

Attracting, developing and retaining talented employees to support the growth of our business is an integral part of our human capital strategy and critical to our long-term success. We continue to seek targeted additions to our staff, although the competition in our industry and in the San Francisco Bay Area where our headquarters is located is significant. The principal purpose of our equity incentive and annual bonus programs is to attract, retain and motivate personnel through the granting of stock-based compensation awards and cash-based performance bonus awards. As a biopharmaceutical company, we recognize the importance of access to high quality healthcare and as such we cover 100% of our employees' monthly healthcare premiums. We offer a package of competitive employee benefits, including 401(k) plan matching contributions and an employee stock purchase plan.

We have a performance development review process in which managers provide regular feedback to assist with the development of our employees, including the use of individual plans to assist with career development. We also invest in the growth and development of our employees through various training and development programs that help build and strengthen our employees' leadership and professional skills. Approximately 20% of our employees are promoted each year. This reflects the quality and readiness of our people to take on new roles, as well as our intentional focus on growing and developing careers, as well as promoting within.

Safeguarding the health and safety of our employees is a top priority. We are committed to providing a safe working environment for all of our employees. Our cross-functional safety committee meets regularly to discuss policies and protocols, strategic planning, business continuity and other matters related to the COVID-19 pandemic and its potential impacts on our company, employees and external stakeholders. In response to the COVID-19 pandemic, we implemented significant changes that we determined were in the best interest of our employees, as well as the communities in which we operate, and which comply with government regulations. This includes having our non-laboratory employees work remotely at least part-time, while implementing additional safety measures for laboratory and other employees continuing critical on-site work. To support our employees personally and professionally, we have Employee Assistance Programs to address employee challenges and needs.

Corporate and Other Information

Our website address is www.protagonist-inc.com. References to our website address do not constitute incorporation by reference of the information contained on the website, and the information contained on the website is not part of this document.

We make available, free of charge on our corporate website, copies of our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, Proxy Statements, and all amendments to these reports, as soon as reasonably practicable after such material is electronically filed with or furnished to the Securities and Exchange Commission ("SEC") pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended ("Exchange Act").

Item 1A. Risk Factors

We have identified the following risks and uncertainties that may have a material adverse effect on our business, financial condition or results of operations. Investors should carefully consider the risks described below before making an investment decision. Our business faces significant risks and the risks described below may not be the only risks we face. If any of these risks occur, our business, results of operations or financial condition could suffer, and the market price of our common stock could decline.

Risks Related to Clinical Development

We are a biopharmaceutical company with no approved products and no historical commercial revenue, which makes it difficult to assess our future prospects and financial results.

We are a biopharmaceutical company with a somewhat limited operating history as a publicly traded company. Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of uncertainty. Our operations to date have been limited to developing our technology, undertaking pre-clinical studies and clinical trials of our pipeline candidates and conducting research to identify additional product candidates. We have not yet successfully developed an approved product or generated revenue from product sales or successfully conducted a pivotal registration trial for one of our product candidates. Consequently, the ability to accurately assess our future operating results or business prospects is significantly more limited than if we had a longer operating history or approved products on the market.

We expect that our financial condition and operating results will fluctuate significantly from period to period due to a variety of factors, many of which are beyond our control, including the success of our programs, decisions by regulatory bodies, actions taken by competitors or current or future licensees or collaborative partners, market conditions and other factors identified in these risk factors. Accordingly, the likelihood of our success must be evaluated in light of many potential challenges and variables associated with a clinical-stage biopharmaceutical company, many of which are outside of our control, and past results, including operating or financial results, should not be relied on as an indication of future results.

We are heavily dependent on the success of our product candidates in clinical development, and if any of these products fail to receive regulatory approval or are not successfully commercialized, our business would be adversely affected.

We currently have no product candidates that are approved for commercial sale, and we may never develop a marketable product. We expect that a substantial portion of our efforts and expenditures over the next few years will be devoted to our current product candidates and the development of other product candidates. We cannot be certain that our product candidates will receive regulatory approval or, if approved, be successfully commercialized. The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of our product candidates will be subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries. In addition, even if approved, our pricing and reimbursement will be subject to further review and discussions with payors. We are not permitted to market any product candidate in the United States until after approval of a new drug application ("NDA") from the FDA, or in any foreign countries until approval by corresponding regulatory authorities. We will need to successfully conduct and complete large, extensive clinical trials in the target patient populations to support a potential application for regulatory approval by the FDA or corresponding regulatory authorities. Those trials, such as our ongoing VERIFY Phase 3 trial evaluating rusfertide for the treatment of PV or subsequent late-stage product candidates, may not demonstrate the safety and efficacy of our product candidates to support a marketing approval in the United States or other jurisdictions.

Our product candidates require additional clinical development, regulatory approval and secure sources of commercial manufacturing supply prior to commercialization. We cannot assure you that our clinical trials for our product candidates will be initiated or completed in a timely manner or successfully, or at all. Further we cannot be certain that we plan to advance any other product candidates into clinical trials. Moreover, any delay or setback in the

development of any product candidate would be expected to adversely affect our business and cause our stock price to fall. For example, our stock price dropped significantly in September 2021 following the announcement of a full clinical hold imposed by the FDA on our rusfertide clinical studies. Our stock price also dropped significantly in April 2022 following the announcement of our voluntary withdrawal of Breakthrough Therapy Designation for rusfertide, and the announcement of topline data from our Phase 2 clinical trial evaluating PN-943 in ulcerative colitis.

Clinical development is a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results. Clinical failure can occur at any stage of clinical development.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical development process. The results of pre-clinical studies and early clinical trials of our product candidates and studies and trials of other products may not be predictive of the results of later-stage clinical trials. Any hypothesis formed from pre-clinical or early clinical observations for any of our product candidates may prove to be incorrect, and the data generated in animal models or observed in limited patient populations may be of limited value and may not be applicable in clinical trials conducted under the controlled conditions required by applicable regulatory requirements.

In addition to our planned pre-clinical studies and clinical trials, we will be required to complete one or more large scale, well-controlled clinical trials to demonstrate substantial evidence of efficacy and safety for each product candidate we intend to commercialize. Further, given the patient populations for which we are developing therapeutics, we expect to have to evaluate long-term exposure to establish the safety of our therapeutics in a chronic-dose setting. We have not yet completed a Phase 3 clinical trial or submitted an NDA. As a result, we have no corporate history or track record of successfully completing these phases of the development cycle. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through pre-clinical studies and initial clinical trials. Clinical trial failures may result from a multitude of factors including, but not limited to, flaws in trial design, dose selection, placebo effect, patient enrollment criteria and failure to demonstrate favorable safety and/or efficacy traits of the product candidate. Based upon negative or inconclusive results, we may decide, or regulators may require us, to conduct additional clinical trials or pre-clinical studies.

We may experience delays in ongoing clinical trials, and we do not know whether planned clinical trials will begin on time, need to be redesigned, enroll patients on time or be completed on schedule, if at all. For example, we initially experienced slower than expected patient enrollment in VERIFY, a global Phase 3 clinical trial of rusfertide in PV. Clinical trials can be delayed for a variety of reasons, including if a clinical trial is modified, suspended or terminated by us. For example, in keeping with our organizational prioritization of rusfertide in PV, plans to initiate trials of rusfertide in additional disease indications have been paused. Clinical trials can also be delayed by the institutional review boards or ethics committees of the institutions in which such clinical trials are being conducted, by a Data Safety Monitoring Board, for such trial or by the FDA or other regulatory authorities. Such authorities may impose a modification, suspension or termination due to a number of factors.

For example, our rusfertide clinical studies were subject to a three-week clinical hold by the FDA beginning in September 2021. The clinical hold was triggered by a non-clinical finding in a 26-week rasH2 transgenic mouse model indicating benign and malignant subcutaneous skin tumors. Also, in April 2022, the FDA indicated that it intended to rescind Breakthrough Therapy Designation for rusfertide in PV. For additional information, see the risk factor entitled "Our product candidates may cause undesirable side effects or have other properties adversely impacting safety that delay or prevent their regulatory approval, restrict their approved labeling, or otherwise limit their commercial opportunity" below.

In addition, there are a significant number of global clinical trials in hematologic disorders that are currently ongoing, especially in Phases 2 and 3, making it highly competitive and challenging to recruit subjects. Additionally, other companies targeting the same patient populations as our clinical trials for such medicines may make it more difficult for us to complete enrollment in our clinical trials. Furthermore, any negative results we may report in clinical trials of our product candidate may make it difficult or impossible to recruit and retain patients in other ongoing or subsequent clinical trials of that same product candidate. Delays or failures in planned patient enrollment or retention

may result in increased costs, program delays or both. In addition, we are subject to risks and uncertainties as a result of the ongoing military conflict in Ukraine and Russia. For example, in 2022 we closed down Clinical trial sites in Russia and Ukraine at which a limited number of subjects were enrolled in our PN-943 Phase 2 IDEAL trial.

If we experience material delays in the completion of any clinical trial, the reduction in remaining patent term would harm the commercial prospects for that product candidate and our ability to generate product revenue from any of these product candidates will be delayed. Any of these occurrences may harm our business, financial condition and prospects significantly.

If we are unable to discover and develop new product candidates, our business will be adversely affected.

As part of our strategy, we seek to discover and develop new product candidates. Research programs to identify appropriate biological targets, pathways and product candidates require substantial scientific, technical, financial and human resources, whether or not any product candidates are ultimately identified. Our research programs may initially show promise in identifying potential product candidates yet fail to yield product candidates for clinical development for many reasons.

Our proprietary peptide platform may not result in any products of commercial value.

We have developed a proprietary peptide technology platform to enable the identification, testing, design and development of new product candidates. Our peptide platform may not yield additional product candidates that enter clinical development and, ultimately, become commercially valuable. Although we expect to continue to enhance the capabilities of our platform by developing and integrating existing and new research technologies, our enhancement and development efforts may not succeed. As a result, we may not be able to advance our drug discovery capabilities as quickly as we expect or identify as many potential drug candidates as we desire.

Our product candidates may cause undesirable side effects or have other properties adversely impacting safety that delay or prevent their regulatory approval, restrict their approved labeling, or otherwise limit their commercial opportunity.

If undesirable side effects or adverse events are caused by our product candidates or by other companies' similar approved drugs or product candidates, then we may elect to, or be required by an independent data monitoring committee or regulatory authorities to, delay or halt our clinical trials. If such side effects or adverse events are sufficiently severe or prevalent, the FDA or comparable foreign regulatory authorities could order us to suspend or cease altogether further development of our product candidates. Even if our product candidates are approved, side effects or adverse events could result in significant delay in or denial of, regulatory approval, restrictive labeling, or potential product liability claims. Moreover, for our product candidates that are in development for indications for which injectable antibody drugs have been approved, clinical trials for those product candidates may need to show a risk/benefit profile that is competitive with those existing products in order to obtain regulatory approval or, if approved, a product label that is favorable for commercialization.

For example, on September 16, 2021 our clinical studies for rusfertide were placed on a full clinical hold by the FDA. On October 8, 2021, the FDA lifted the full clinical hold and dosing in all clinical studies of rusfertide could be resumed after we provided the FDA with all requested information as the basis for a Complete Response and subsequent removal of the clinical hold. In particular, we provided the requested individual patient clinical safety reports, updated the investigator brochure and patient informed consent forms, performed a comprehensive review of the most recent safety database, and included new safety and stopping rules in the study protocols. The clinical hold was initially triggered by a non-clinical finding in a 26-week rasH2 transgenic mouse model indicating benign and malignant subcutaneous skin tumors. The rasH2 signal also prompted a re-examination of the four cases of cancer observed across all rusfertide clinical trials involving over 160 patients, and a comprehensive review of the safety database, including cases of suspected unexpected serious adverse reactions.

We have focused our limited resources to pursue particular product candidates and indications, and consequently, we may 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 have historically focused on research programs and product candidates mainly on the development of rusfertide, the product candidates subject to our Janssen collaboration and, through early 2022, PN-943. Going forward, we have no plans to devote further resources to PN-943 as part of our ongoing commitment to optimize and focus resources toward our rusfertide program in PV. In addition, in keeping with our organizational prioritization of rusfertide in PV, plans to initiate trials of rusfertide in additional disease indications have been paused. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. 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 partnerships, 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.

Risks Related to our Financial Position and Capital Requirements

We have incurred significant losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future. We have never generated any revenue from product sales and may never be profitable.

We have incurred significant operating losses every year since inception and expect to continue to incur operating losses for the foreseeable future. As of December 31, 2022, we had an accumulated deficit of $536.8 million. We expect to continue to incur significant research, development and other expenses related to our ongoing operations and product development. As a result, we expect to continue to incur losses in the future as we continue our development of, and seek regulatory approvals for, our product candidates.

We do not anticipate generating revenue from sales of products for a number of years, if ever, and we have not yet successfully completed registrational or pivotal clinical trials for our product candidates. If any of our product candidates fail in clinical trials or do not gain regulatory approval or fail to achieve market acceptance, we may never become profitable. Revenue we generate from our collaboration with Janssen, and any future collaboration arrangements may not be sufficient to sustain our operations. Failure to become and remain profitable may adversely affect the market price of our common stock and our ability to raise capital and continue operations.

We expect to require substantial additional funding, which may not be available to us on acceptable terms, or at all.

Our operations have consumed substantial amounts of cash since inception. Developing pharmaceutical product candidates, including conducting pre-clinical studies and clinical trials, is expensive. We expect to require substantial additional future capital in order to complete clinical development and, if we are successful, to commercialize any of our current product candidates. Further, in the event that the Restated Agreement with Janssen is terminated, we may not receive any additional fees or milestone payments under that agreement. Absent the funding support obtained under the Restated Agreement, our further development of the collaboration product candidates would require significant additional capital from us, or the establishment of alternative collaborations with third parties, which may not be possible.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of $237.4 million. Based upon our current operating plan and expected expenditures, we believe that our existing cash, cash equivalents, and marketable securities will be sufficient to fund our operations for at least the next 12 months. However, we expect that we will need to have access to substantial additional funds in the future in order to complete clinical development or commercialize our product candidates to a point where our operations generate net cash inflows.

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

We may seek additional funding through a combination of equity offerings, including use of our ATM facility, debt financings, collaborations and/or licensing arrangements. Additional funding may not be available to us on acceptable terms, or at all. Our ability to raise additional capital may be adversely impacted by adverse economic conditions and market volatility. The incurrence of indebtedness and/or the issuance of certain equity securities could result in fixed payment obligations and could also result in certain additional restrictive covenants, such as limitations on our ability to incur debt and/or issue additional equity, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. In addition, the issuance of additional equity securities by us, or the possibility of such issuance, may cause the market price of our common stock to decline. In the event that we enter into additional collaborations and/or licensing arrangements in order to raise capital, we may be required to accept unfavorable terms, including relinquishing or licensing to a third party on unfavorable terms our rights to our proprietary technology platform or product candidates. To the extent that we raise additional capital through the sale of equity securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. If we issue common stock or securities convertible into common stock, our common stockholders would experience additional dilution and, as a result, our stock price may decline.

Risks Related to our Reliance on Third Parties

If Janssen does not elect to continue the development of JNJ-2113, our business and business prospects would be adversely affected.

JNJ-2113 (formerly known as PN-235), the product candidate in development pursuant to our Janssen collaboration, may prove to have undesirable or unintended side effects or other characteristics adversely affecting its safety, efficacy or cost effectiveness that could prevent or limit its approval for marketing and successful commercial use, or that could delay or prevent the commencement and/or completion of clinical trials. Under the terms of the Restated Agreement with Janssen, Janssen may terminate the agreement for convenience and without cause on written notice of a certain period. In addition, prior to any termination of the agreement, Janssen will generally have control over the further clinical development of JNJ-2113 and any other licensed compounds. Janssen's decisions with respect to such development will affect the timing and availability of potential future payments under the agreement, if any. For example, during the fourth quarter of 2021, following a pre-specified interim analysis criteria, a portfolio decision was made by Janssen to stop further development of both PTG-200 and PN-232 in favor of JNJ-2113. If the Restated Agreement with Janssen is terminated early, or if Janssen's development activities are terminated early or suspended for an extended period of time, or are otherwise unsuccessful, our business and business prospects would be materially and adversely affected.

We may have disagreements with Janssen during the term of the Janssen License and Collaboration Agreement, and if they are not settled amicably or in the favor of Protagonist, the result may harm our business.

We are subject to the risk of possible disagreements with Janssen regarding the development of JNJ-2113 or other matters under the Restated Agreement with Janssen, such as the interpretation of the agreement or ownership of proprietary rights. Also, because the period of collaborative development under the agreement has ended, Janssen has sole decision-making authority for product candidates resulting from the collaboration, which could lead to disputes with Janssen. Disagreements with Janssen could lead to litigation or arbitration, which would be expensive and would be time-consuming for our management and employees.

We may not be successful in obtaining or maintaining development and commercialization collaborations, any collaboration arrangements we enter into in the future may not be successful.

Other than our Restated Agreement with Janssen, we have no active collaborations for any of our product candidates. Even if we establish other collaboration arrangements, any such collaboration may not ultimately be

successful, which could have a negative impact on our business, results of operations, financial condition and growth prospects. If we enter into collaborations limited to certain territories, we may not maintain significant rights or control of future development and commercialization of any product candidate subject to the collaboration and potential disputes could develop in the future over the terms of the collaboration and the respective rights of the parties.

If our strategic collaborations do not result in the successful development and commercialization of product candidates or if one of our collaborators fails to act under the collaboration agreement or terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the applicable collaboration agreement. In addition, if a collaboration is terminated, it may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

We rely on third parties to conduct our pre-clinical studies and clinical trials. If these third parties do not successfully carry out their contractual obligations or do not meet regulatory requirements or expected deadlines, we may not be able to obtain timely regulatory approval for or commercialize our product candidates and our business could be substantially harmed.

We have relied upon and plan to continue to rely upon third-party contract research organizations ("CROs") to execute, monitor and manage clinical trials and collect data for our pre-clinical studies and clinical programs. We control only certain aspects of their activities. We and our CROs are required to comply with GCPs, which are regulations and guidelines promulgated by the FDA, the EMA and comparable foreign regulatory authorities for all of our product candidates in clinical development. If we or any of our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or comparable foreign regulatory authorities may not accept the data or require us to perform additional clinical trials before considering our filing for regulatory approval or approving our marketing application. In addition, significant portions of the clinical studies for our product candidates are expected to be conducted outside of the United States, which will make it more difficult for us to monitor CROs and perform visits of our clinical trial sites (particularly during the ongoing pandemic) and will force us to rely heavily on CROs to ensure the proper and timely conduct of our clinical trials and compliance with applicable regulations, including GCPs.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase substantially and our ability to generate revenue could be delayed significantly.

We face a variety of manufacturing risks and rely on third parties to manufacture our drug substance and clinical drug product and we intend to rely on third parties to produce commercial supplies of any approved product candidate.

We rely on contract manufacturers to manufacture and provide product for us that meets applicable regulatory requirements. We do not currently have, nor do we plan to develop, the infrastructure or capability internally to manufacture our drug supplies and we expect to continue to depend on contract manufacturers for the foreseeable future. As we proceed with the development and potential commercialization of our product candidates, we will need to increase the scale at which the drug is manufactured which will require the development of new manufacturing processes to potentially reduce the cost of goods. We will rely on our internal process research and development efforts and those of contract manufacturers to develop the good manufacturing processes ("GMPs") required for cost-effective, large-scale production. If we and our contract manufacturers are not successful in converting to commercial-scale manufacturing, then our product costs may not be competitive and the development and/or commercialization of our product candidates would be materially and adversely affected. Moreover, our contract manufacturers are the sole source of supply for our clinical product candidates. If we were to experience an unexpected loss of supply for any reason, whether as a result of

manufacturing, supply or storage issues, natural disasters, the COVID-19 pandemic or otherwise, we could experience delays, disruptions, suspensions or termination of our clinical trial and planned development program, or be required to restart or repeat, any ongoing clinical trials.

We also rely on our contract manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidates for our clinical trials. There are a limited number of suppliers for raw materials that our vendors use to manufacture our drugs and there may be a need to assess alternate suppliers to prevent a possible disruption of the manufacture of the materials necessary to produce our product candidates for our clinical trials, and if approved, for commercial sale. Moreover, we currently do not have any agreements for the commercial production of these raw materials. Although we generally do not begin a clinical trial unless we believe we have a sufficient supply of a product candidate to complete the clinical trial, any significant delay in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical trial due to the need to replace a contract manufacturer or other third-party manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of our product candidates.

Risks Related to Regulatory Approval

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy and time consuming, and if we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

Our business is substantially dependent on our ability to successfully develop, obtain regulatory approval for and then successfully commercialize our product candidates. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA, the EMA or any other foreign regulatory authority, and we may never receive such regulatory approval for any of our product candidates. The time required to obtain approval by the FDA and comparable foreign authorities is difficult to predict, typically takes many years following the commencement of clinical trials and depends upon numerous factors. Approval policies, regulations and the types and amount of clinical and manufacturing data necessary to gain approval may change during the course of clinical development and may vary among jurisdictions. We have not obtained regulatory approval for any product candidate and it is possible that none of our existing product candidates or any product candidates we have in development or may seek to develop in the future will ever obtain regulatory approval.

Our product candidates could fail to receive regulatory approval for many reasons, including the following:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials, or our interpretation of the data submitted in support of regulatory approval:
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication or that a product candidate's clinical and other benefits outweigh its safety risks;
- the results of clinical trials may fail to achieve the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- the data collected from pre-clinical studies and clinical trials of our product candidates may not be sufficient to support the submission of an NDA, supplemental NDA, or other regulatory submissions necessary to obtain regulatory approval;
- we or our contractors may not meet the GMP and other applicable requirements for manufacturing processes, procedures, documentation and facilities necessary for approval by the FDA or comparable foreign regulatory authorities; and

- changes to the approval policies or regulations of the FDA or comparable foreign regulatory authorities with respect to our product candidates may result in our clinical data becoming insufficient for approval.

In addition, even if we were to obtain regulatory approval, regulatory authorities may approve our product candidates for fewer or more limited indications than what we requested approval for, may include safety warnings or other restrictions that may negatively impact the commercial viability of our product candidates, including the potential for a favorable price or reimbursement at a level that we would otherwise intend to charge for our products. Likewise, regulatory authorities may grant approval contingent on the performance of costly post-marketing clinical trials or the conduct of an expensive risk-evaluation and mitigation system, which could significantly reduce the potential for commercial success or viability of our product candidates. Any of the foregoing possibilities could materially harm the prospects for our product candidates and business and operations.

We may fail to obtain orphan drug designations from the FDA and/or the EMA for our product candidates, as applicable, and even if we obtain such designations, we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity.

Our strategy includes filing for orphan drug designation where available for our product candidates. Rusfertide has received orphan drug designation for the treatment of patients with PV from the FDA and the EMA. Despite this designation, we may be unable to maintain the benefits associated with orphan drug status, including market exclusivity. We may not be the first to obtain regulatory approval of a product candidate for a given orphan-designated indication. In addition, exclusive marketing rights in the United States may be limited if we seek approval for an indication broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if we are unable to assure sufficient quantities of the product to meet patient needs. Further, even if we obtain orphan drug designation exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties may receive and be approved for the same condition, and only the first applicant to receive approval for a given active ingredient will receive the benefits of marketing exclusivity. Even after an orphan-designated product is approved, the FDA can subsequently approve a later drug with the same active moiety for the same condition if the FDA concludes that the later drug is clinically superior if it is shown to be safer, more effective or makes a major contribution to patient care.

Risks Related to Commercialization of our Product Candidates

We currently have no marketing and sales organization. To the extent any of our product candidates for which we maintain commercial rights is approved for marketing, if we are unable to establish marketing and sales capabilities or enter into agreements with third parties to market and sell our product candidates, we may not be able to effectively market and sell any products or generate product revenue.

We currently do not have a marketing or sales organization for the marketing, sales and distribution of pharmaceutical products. In order to commercialize any of our product candidates that receive marketing approval, we will have to build marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so. In the event of successful development of any of our product candidates, we may elect to build a targeted specialty sales force which will be expensive and time consuming. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of these products. With respect to our product candidates, we may choose to partner with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems, and in the case of the Restated Agreement with Janssen, we may elect to exercise our Co-Detailing Option (allows us to elect to provide up to 30% of the selling effort in the United States for any IL-23R antagonist compounds approved for commercial sale), which would require us to establish a U.S. sales team. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future revenue will be materially and adversely impacted.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may obtain.

In the United States and some foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. 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 therapies, which could result in reduced demand for us.

Legislative and regulatory proposals have also been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements. See Item 1. "Business—Government Regulation—Coverage and Reimbursement" for additional information.

We currently conduct, and intend to continue to conduct, a substantial portion of the clinical trials for our product candidates outside of the United States. If approved, we may commercialize our product candidates abroad. We will thus be subject to the risks of doing business outside of the United States.

We currently conduct, and intend to continue to conduct, a substantial portion of our clinical trials outside of the United States and, if approved, we intend to also market our product candidates outside of the United States. We are thus subject to risks associated with doing business outside of the United States. Our business and financial results in the future could be adversely affected due to a variety of factors associated with conducting development and marketing of our product candidates, if approved, outside of the United States, including varying medical standards and practices, geopolitical risks, uncertainty around intellectual property protection, and regulatory risks, such as compliance with the Foreign Corrupt Practices Act. If we are unable to anticipate and address these risks properly, our business and financial results will be harmed.

We may fail or elect not to commercialize our product candidates, even if approved.

We cannot be sure that, if our clinical trials for any of our product candidates are successfully completed, we will be able to submit an NDA to the FDA or that any NDA we submit will be approved by the FDA in a timely manner, if at all. After completing clinical trials for a product candidate in humans, a drug dossier is prepared and submitted to the FDA as an NDA, and includes all pre-clinical studies and clinical trial data relevant to the safety and effectiveness of the product at the suggested dose and duration of use for the proposed indication as well as manufacturing information, in order to allow the FDA to review such drug dossier and to consider a product candidate for approval for commercialization in the United States. If we are unable to submit an NDA with respect to any of our current product candidates, if any NDA we submit is not approved by the FDA, or we elect not to file an NDA, or if we are unable to obtain any required state and local distribution licenses or similar authorizations, we will be unable to commercialize that product. The FDA can and does reject NDAs and require additional clinical trials, even when product candidates achieve favorable results in Phase 3 clinical trials. Also, we may be subject to pricing pressures from competitive products that could make it difficult or impossible for us to commercialize the product candidate successfully. If we fail to commercialize any of our product candidates, our business, financial condition, results of operations and prospects may be materially and adversely affected.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, third-party payors and others in the medical community.

We or our collaboration partners in any potential commercial launch of our product candidates may not be successful in achieving widespread patient or physician awareness or acceptance of such product candidate. Even though we expect that our product candidate will be priced responsibly, if approved, there is no guarantee that it or any other product that we bring to the market directly or through a strategic partner will gain market acceptance by physicians, patients, third-party payors and others in the medical community. The degree of market acceptance of any of our product candidates, if approved for commercial sale, will depend on a number of factors, including but not limited to:

- the safety and efficacy of the product in clinical trials, and potential advantages over competing treatments;
- the publication of unfavorable safety or efficacy data concerning our product by third parties;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the clinical indications for which approval is granted;
- recognition and acceptance of our product candidates over our competitors' products;
- prevalence of the disease or condition for which the product is approved;
- the cost of treatment, particularly in relation to competing treatments;
- the willingness of the target patient population to try our therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- the extent to which the product is approved for inclusion on formularies of hospitals and managed care organizations;
- publicity concerning our products or competing products and treatments;
- the extent to which third-party payors provide coverage and adequate reimbursement for the product candidate, or any other product candidates we may pursue, if approved;
- our ability to maintain compliance with regulatory requirements; and
- labeling or naming imposed by FDA or other regulatory agencies.

Even if a product candidate we may develop in the future displays an equivalent or more favorable efficacy and safety profile in pre-clinical and clinical trials, market acceptance of the product candidate will not be fully known until after it is launched and may be negatively affected by a potential poor safety experience and the track record of other product candidates. Our efforts, or those of any strategic licensing or collaboration partner, to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources, may be under-resourced compared to large well-funded pharmaceutical entities and may never be successful. If ay product candidates we may develop in the future are approved but fail to achieve an adequate level of acceptance by physicians, patients, third-party payors and others in the medical community, we will not be able to generate sufficient revenue to become or remain profitable.

Risks Related to our Business and Industry

We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We have competitors worldwide, including major multinational pharmaceutical companies, biotechnology companies, specialty pharmaceutical and generic pharmaceutical companies as well as universities and other research institutions.

Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, and experienced marketing and manufacturing organizations. As a result, these companies may obtain regulatory approval more rapidly than we are able and may be more effective in selling and marketing their products. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Competition may increase further as a result of advances in the commercial applicability of newer technologies and greater availability of capital for investment in these industries. Our competitors may succeed in developing, acquiring or licensing, on an exclusive basis, pharmaceutical products that are easier to develop, more effective or less costly than any product candidates that we are currently developing or that we may develop. If approved, our product candidates are expected to face competition from commercially available drugs as well as drugs that are in the development pipelines of our competitors.

Pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make our product candidates less competitive. In addition, any new product that competes with an approved product must demonstrate advantages in efficacy, convenience, tolerability or safety in order to overcome price competition and to be commercially successful. If our competitors succeed in obtaining FDA, EMA or other regulatory approval or discovering, developing and commercializing drugs before we do, there would be a material adverse impact on the future prospects for our product candidates and business. For example, in November 2021, the FDA approved a Biologics License Application for ropeginterferon alfa-2b for use in treatment for patients with PV in the absence of symptomatic splenomegaly from PharmaEssentia Corporation, the manufacturer of the novel pegylated interferon. We also face competition in certain instances from the existing standards of care, which may be significantly less expensive than our expected drug prices. For example, one widely used treatment for patients is phlebotomy and/or chelation therapy. While patients may not like therapies that involve frequent blood draws, these therapies are inexpensive and may present pricing challenges for us if our drug candidates are successfully developed and approved. See Item 1. “Business—Competition” for additional information.

The COVID-19 pandemic has and could continue to adversely impact our business, including our ongoing and planned clinical trials and pre-clinical and discovery research.

The extent to which the COVID-19 pandemic will continue to impact our business is uncertain and cannot be predicted. The pandemic’s impact on our business will depend on a variety of factors, including the timing, extent, effectiveness and durability of vaccine programs or other treatments, new or continuing travel and other restrictions and public health measures, such as social distancing, business closures or disruptions, and the development and spread of COVID-19 variants. As the COVI-19 pandemic evolves, we could experience additional disruptions or increased expenses that may adversely impact our business, including:

- delays or difficulties in enrolling patients in our ongoing clinical trials and our future clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff, or maintaining ongoing operations at such sites; and
- delays in manufacturing, receiving the supplies, materials and services needed to conduct clinical trials and pre-clinical research.

While the extent of the impact of the COVID-19 pandemic on our business and financial results is uncertain, a continued and prolonged public health crisis such as the COVID-19 pandemic could have a material negative impact on our business, financial condition, and operating results.

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

As has been widely reported, we are currently operating in a period of economic uncertainty and capital markets disruption, which has been significantly impacted by domestic and global monetary and fiscal policy, geopolitical instability, including an ongoing military conflict between Russia and Ukraine, the rising tensions between China and Taiwan, and historically high domestic and global inflation. In particular, the conflict in Ukraine has exacerbated market disruptions, including significant volatility in commodity prices, as well as supply chain interruptions, and has contributed to record inflation globally. The U.S. Federal Reserve and other central banks may be unable to contain inflation through more restrictive monetary policy and inflation may increase or continue for a prolonged period of time. Inflationary factors, such as increases in the cost of clinical supplies, interest rates, overhead costs and transportation costs may adversely affect our operating results. We continue to monitor these events and the potential impact on our business. Although we do not believe that inflation has had a material impact on our financial position or results of operations to date, we may be adversely affected in the future due to domestic and global monetary and fiscal policy, supply chain constraints, consequences associated with COVID-19 and the ongoing conflict between Russia and Ukraine, and such factors may lead to increases in the cost of manufacturing our product candidates and delays in initiating trials. In addition, global credit and financial markets have experienced extreme volatility and disruptions in the past several years and the foregoing factors have led to and may continue to cause diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, uncertainty about economic stability and increased inflation.

There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. A future recession or market correction or other significant geopolitical events could materially affect our business and the value of our common stock. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals.

If we fail to comply with state and federal healthcare regulatory laws, we could face substantial penalties, damages, fines, disgorgement, integrity oversight and reporting obligations, exclusion from participation in governmental healthcare programs, and the curtailment of our operations, any of which could adversely affect our business, operations, and financial condition.

Healthcare providers, including physicians, and third-party payors will play a primary role in the recommendation and prescription of any future product candidates we may develop or any product candidates for which we obtain marketing approval. Our arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may affect the business or financial arrangements and relationships through which we would market, sell and distribute our products. Even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. The laws that may affect our ability to operate include, but are not limited to:

- the federal Anti-Kickback Statute;
- the federal false claims laws, including the False Claims Act;

- the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA");
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and their implementing regulations, which also imposes obligations, including mandatory contractual terms, on HIPAA-covered entities, their business associates as well as their covered subcontractors with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal civil monetary penalties statute;
- the federal Physician Payments Sunshine Act; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws.

Further, the ACA, among other things, amended the intent requirements of the federal Anti-Kickback Statute and certain criminal statutes governing healthcare fraud. Any violations of these laws, or any action against us for violation of these laws, even if we successfully defend against it, could result in a material adverse effect on our reputation, business, results of operations and financial condition.

We have entered into consulting and scientific advisory board arrangements with physicians and other healthcare providers, including some who could influence the use of our product candidates, if approved. While we have worked to structure our arrangements to comply with applicable laws, because of the complex and far-reaching nature of these laws, regulatory agencies may view these transactions as prohibited arrangements that must be restructured, or discontinued, or for which we could be subject to other significant penalties. We could be adversely affected if regulatory agencies interpret our financial relationships with providers who may influence the ordering of and use our product candidates, if approved, to be in violation of applicable laws.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform. Federal and state enforcement bodies have continued to increase their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of significant investigations, prosecutions, convictions and settlements in the healthcare industry. Additionally, as a result of these investigations, healthcare providers and entities may have to agree to additional onerous compliance and reporting requirements as part of a consent decree or corporate integrity agreement. Any such investigation or settlement could significantly increase our costs or otherwise have an adverse effect on our business.

If our operations are found to be in violation of any of these laws or any other governmental laws and regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, integrity oversight and reporting obligations, exclusion from government funded healthcare programs, such as Medicare and Medicaid, disgorgement, contractual damages, reputational harm, diminished profits and the curtailment or restructuring of our operations. If, and to the extent that, Janssen or we are unable to comply with these regulations, our ability to earn potential royalties from worldwide net sales of Janssen collaboration product candidates would be materially and adversely impacted. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. The imposition of any of these penalties or other commercial limitations could negatively impact our collaboration with Janssen or cause Janssen to terminate the Restated Agreement with Janssen, either of which would materially and adversely affect our business, financial condition and results of operations.

Our future success depends on our ability to retain our executive officers and to attract, retain and motivate qualified personnel. If we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

We are highly dependent on our existing senior management team. The loss of the services of any of our executive officers or other key employees and our inability to find suitable replacements would harm our research and

development efforts, our collaboration efforts, as well as our business, financial condition and prospects. Our success also depends on our ability to continue to attract, retain and motivate highly skilled and experienced personnel with scientific, medical, regulatory, manufacturing, marketing, sales, general and administrative and management training and skills.

We may not be able to attract or retain qualified personnel in the future due to the intense competition for a limited number of qualified personnel among biopharmaceutical, biotechnology, pharmaceutical and other businesses. Many of the other biopharmaceutical and pharmaceutical companies that we compete against for qualified personnel have greater financial and other resources, different risk profiles and a longer history in the industry than we do. Many are located in areas of the country with lower costs of living. Additionally, the United States has recently experienced historically high levels of inflation and an acute workforce shortage generally, which has created a hyper-competitive wage environment that may increase our operating costs. Any or all of these factors may limit our ability to continue to attract and retain high quality personnel, which could negatively affect our ability to successfully develop and commercialize product candidates and to grow our business and operations as currently contemplated.

We expect to expand the size of our organization in the future, and we may experience difficulties in managing this growth.

As our development and commercialization plans and strategies develop, we expect to need additional managerial, operational, scientific, sales, marketing, research, development, regulatory, manufacturing, financial and other resources. In addition, as our operations expand, we expect that we will need to manage relationships with strategic collaborators, CROs, contract manufacturers, suppliers, vendors and other third parties. Our future financial performance and our ability to develop and commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. We may not be successful in accomplishing these tasks in growing our company, and our failure to accomplish any of them could adversely affect our business and operations.

Significant disruptions of information technology systems or breaches of data security could adversely affect our business.

Our business is increasingly dependent on critical, complex and interdependent information technology systems, including Internet-based systems, to support business processes as well as internal and external communications. The size and complexity of our internal computer systems and those of our CROs, contract manufacturers, collaboration partner, and other third parties on which we rely may make them potentially vulnerable to breakdown, telecommunications and electrical failures, malicious intrusion such as ransomware and computer viruses that may result in the impairment of key business processes. Our systems are potentially vulnerable to data security breaches, by employees or others, that may expose sensitive data to unauthorized persons. Such data security breaches could lead to the loss of trade secrets or other intellectual property or could lead to the public exposure of personally identifiable information (including sensitive personal information) of our employees, collaborators, clinical trial patients, and others. A malicious intrusion, email compromise or other data security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to liability under laws and regulations that protect personal data, resulting in increased costs or loss of revenue. If we are unable to prevent such data security breaches or privacy violations or implement satisfactory remedial measures, our operations could be disrupted, and we may suffer loss of reputation, financial loss and other regulatory penalties.

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 materials, and 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.

Our employees, independent contractors, principal investigators, consultants and vendors 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 that our employees, independent contractors, principal investigators, consultants or vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (i) FDA laws and regulations or those of comparable foreign regulatory authorities, (ii) manufacturing standards, (iii) federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations established and enforced by comparable foreign regulatory authorities, or (iv) laws that require the true, complete and accurate reporting of financial information or data. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability and a breach of warranties. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to stop development or, if approved, limit commercialization of our product candidates.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the development or commercialization of our product candidates. We currently carry clinical trial liability insurance for our clinical trials. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

Our headquarters is located near known earthquake fault zones. The occurrence of an earthquake, fire or any other catastrophic event could disrupt our operations or the operations of third parties who provide vital support functions to us, which could have a material adverse effect on our business and financial condition.

We and some of the third-party service providers on which we depend for various support functions are vulnerable to damage from catastrophic events, such as power loss, natural disasters, terrorism, pandemics and similar unforeseen events beyond our control. Our corporate headquarters, including our laboratory facilities, are located in the San Francisco Bay Area, which in the past has experienced severe earthquakes and fires. We do not carry earthquake insurance. Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects.

The insurance coverage and reimbursement status of newly approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for our product candidates could limit our ability to generate revenue.

The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford medications and therapies. Sales of any of our product candidates that receive marketing approval will depend substantially, both in the United States and internationally, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain adequate pricing that will allow us to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products as increasingly high barriers are being erected to the entry of new products into the healthcare markets. Coverage and reimbursement can differ significantly from payor to payor. It is difficult to predict what CMS will decide with respect to reimbursement for novel products such as ours since there is no body of established practices and precedents for these new products.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe, Canada and other countries may cause us to price our product candidates on less favorable terms than we currently anticipate. In many countries, particularly the countries of the EU, 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. In general, the prices of products under such systems are substantially lower than in the United States. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenues and profits.

Risks Related to our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to our product candidates and technologies, we may not be able to compete effectively in our markets.

We rely upon a combination of patent protection, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates and technologies. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. We may or may not file or prosecute all necessary or desirable patent applications. The patent applications that we own or license may fail to result in issued patents in the United States or in other foreign countries, or they may fail to result in issued patents with claims that cover our product candidates or technologies in the United States or in other foreign countries. Any failure to identify relevant prior art relating to a patent or patent applications can invalidate a patent or prevent a patent from issuing. Even if patents have been issued, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. Furthermore, even if they are unchallenged, our patent and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates and technologies, or prevent others from designing around our claims.

If the breadth or strength of protection provided by our patents is challenged, or if they fail to provide meaningful exclusivity for our product candidates, it could prevent us from asserting exclusivity over the covered product and allow generic competition. We cannot offer any assurances about which, if any, of our patent applications will issue, the breadth of any such issued patent, or whether any issued patents will be found invalid and unenforceable or will be

threatened by third parties. Any successful opposition or other challenge to our patents or patent applications could significantly diminish the commercial prospects of any products that we develop.

In addition, patents have a limited lifespan. In the United States and in many other countries, the natural expiration of a patent is generally 20 years after it is filed, and once any patents covering a product expire, generic competitors may enter the market. Our granted U.S. patent covering rusfertide expires in 2034, but is eligible for extension of up to five years for a portion of the time spent in development. Although the life of a patent can be increased based on certain delays caused by the U.S. Patent and Trademark Office (the "PTO"), this increase can be reduced or eliminated based on certain delays caused by the patent applicant during patent prosecution. If we encounter delays in our clinical trials or in gaining regulatory approval, the period of time during which we could market any of our product candidates under patent protection, if approved, would be reduced.

We may not be able to protect our intellectual property rights throughout the world. Filing, prosecuting and defending patents on all of our product candidates throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States may be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights, including trade secrets, to the same extent as federal and state laws of the United States and many countries limit the enforceability of patents against third parties, including government agencies or government contractors.

Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as in the United States. These products may compete with our products in jurisdictions where we do not have any issued patents and our patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing. Also, if our trade secrets are disclosed in a foreign jurisdiction, competitors worldwide could have access to our proprietary information and we may be without satisfactory recourse. Such disclosure could have a material adverse effect on our business.

We also rely on trade secret protection and confidentiality agreements to protect proprietary scientific, business and technical information and know-how that is not or may not be patentable or that we elect not to patent. For example, we primarily rely on trade secrets and confidentiality agreements to protect our peptide therapeutics technology platform. Any disclosure to or misappropriation by third parties of our confidential proprietary information could enable competitors to quickly duplicate or surpass our technological achievements, thus eroding our competitive position in our market. If we are unable to protect the confidentiality of our trade secrets and proprietary know-how or if competitors independently develop viable competing products, our business and competitive position may be harmed.

Although we require all of our employees to assign their inventions to us, and endeavor to execute confidentiality agreements with all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how and other confidential information related to such technology, we cannot be certain that we have executed such agreements with all third parties who may have helped to develop our intellectual property or who had access to our proprietary information, nor can be we certain that our agreements will not be breached. If any of the parties to these confidentiality agreements breaches or violates the terms of such agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets as a result.

Even if we are able to adequately protect our trade secrets and proprietary information, our trade secrets could otherwise become known or could be independently discovered by our competitors. If our trade secrets are not adequately protected so as to protect our market against competitors' products, others may be able to exploit our proprietary peptide product candidate discovery technologies to identify and develop competing product candidates, and thus our competitive position could be adversely affected, as could our business.

We may be involved in lawsuits and other legal proceedings to protect or enforce our intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our issued patents or any patents issued as a result of our pending or future patent applications. 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 not valid or is unenforceable or may refuse to stop the other party in such infringement proceeding 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 or defense proceedings could put one or more of our patents at risk of being invalidated, held unenforceable or interpreted narrowly, and could put any of our patent applications at risk of not yielding an issued patent.

Issued patents and patent applications may be challenged in the courts and in the patent office in the United States and abroad. An adverse determination in any such challenge could prevent the issuance of, reduce the scope of, invalidate or render unenforceable our patent rights, result in the loss of exclusivity, or limit our ability to stop others from using or commercializing our platform technology and products. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

Any issued patents covering our product candidates, including any patent that may issue as a result of our pending or future patent applications, could be found invalid or unenforceable if challenged in court in the United States or abroad.

As more groups become engaged in scientific research and product development in fields related to our product candidates, such as hepcidin mimetics or IL-23R, the risk of our patents, or patents that we have in-licensed, being challenged through patent interferences, derivation proceedings, oppositions, re-examinations, litigation or other means will likely increase. An adverse outcome in a patent dispute could have a material adverse effect on our business by:

- causing us to lose patent rights in the relevant jurisdiction(s);
- subjecting Janssen or us to litigation, or otherwise preventing the commercialization of product candidates in the relevant jurisdiction(s); or
- requiring Janssen or us to obtain licenses to the disputed patents, cease using the disputed technology or develop or obtain alternative technologies.

An adverse outcome in a patent dispute could severely harm our collaboration with Janssen or cause Janssen to terminate the Restated Agreement.

Litigation or other legal proceedings relating to intellectual property claims, with or without merit, are unpredictable and generally expensive and time-consuming and, even if resolved in our favor, are likely to divert significant resources from our core business, including distracting 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 market price of our common stock. 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. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating or from successfully challenging our intellectual property rights. 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.

Third party claims of intellectual property infringement may prevent or delay our drug discovery and development efforts.

Our commercial success depends in part on our ability to develop, manufacture, market and sell our drug candidates and use our proprietary technologies without infringing or otherwise violating the patents and proprietary rights of third parties. Numerous third-party U.S. and foreign issued patents and pending patent applications exist in the fields in which we are developing product candidates, and there may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates and technologies.

Third parties may initiate legal proceedings against us alleging that we are infringing or otherwise violating their patent or other intellectual property rights. Given the vast number of patents in our field of technology, marketing of our product candidates or practice of our technologies could infringe existing patents or patents granted in the future. There may be applications now pending of which we are unaware that may later result in issued patents that may be infringed by the practice of our peptide therapeutics technology platform or the manufacture, use or sale of our product candidates. If any third-party patents were to be held by a court of competent jurisdiction to cover the manufacturing process of any of our product candidates, any molecules formed during the manufacturing process or any final product or formulation itself, the holders of any such patents may be able to block our ability to commercialize such product candidate unless we obtained a license under the applicable patents, or until such patents expire. As our industry expands and more patents are issued, the risk increases that our product candidates or technologies may give rise to claims of infringement of the patent rights of others.

Parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to commercialize our product candidates. Even if we are successful in defending against any infringement claims, litigation is expensive and time-consuming and is likely to divert management's attention and substantial resources from our core business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, limit our uses, pay royalties or redesign our infringing product candidates, which may be impossible or require substantial time and monetary expenditure. We may choose to seek, or may be required to seek, a license from the third-party patent holder and would most likely be required to pay license fees or royalties or both, each of which could be substantial. These licenses may not be available on commercially reasonable terms, however, or at all. Even if we were able to obtain a license, the rights we obtain may be nonexclusive, which would provide our competitors access to the same intellectual property rights upon which we are forced to rely. Furthermore, even in the absence of litigation, we may need to obtain licenses from third parties to advance our research or allow commercialization of our product candidates, and we have done so from time to time. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In such an event, we would be unable to further practice our technologies or develop and commercialize any of our product candidates at issue, which could harm our business significantly.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties or that our employees have wrongfully used or disclosed alleged trade secrets of former or other employers.

Many of our employees and consultants, including our senior management and our scientific founders, have been employed or retained at universities or by other biotechnology or pharmaceutical companies, including potential competitors. Some of our employees and consultants, including each member of our senior management and each of our scientific founders, executed proprietary rights, non-disclosure and non-competition agreements in connection with such previous employment or retention. We may be subject to claims that we or these employees, consultants or independent contractors have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such employee's or consultant's former or other employer. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

We may be subject to claims challenging the inventorship or ownership of our issued patents, any patents issued as a result of our pending or future patent applications and other intellectual property.

We may be subject to claims that former employees, collaborators or other third parties have an ownership interest in our issued patents, any patents issued as a result of our pending or future applications or other intellectual property. We have had in the past, and we may also have in the future, ownership disputes arising, for example, from conflicting obligations of consultants or others who are involved in developing our product candidates and technologies. Litigation may be necessary to defend against these and other claims.

In addition, some of our intellectual property rights were generated through the use of U.S. government funding and are therefore subject to certain federal regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future product candidates pursuant to the Bayh-Dole Act of 1980 and implementing regulations. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us or our licensors to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party in certain circumstances (also referred to as "march-in rights").

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we expect to rely on third parties in the development and manufacture of our product candidates, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have an adverse effect on our business and results of operations.

Intellectual property rights do not necessarily address all potential threats to our business.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business. The following examples are illustrative:

- others may be able to make compounds or formulations that are similar to our product candidates, but that are not covered by the claims of any patents that we own, license or control;
- we or any strategic partners might not have been the first to make the inventions covered by the issued patents or pending patent applications that we own;
- we may not have been the first to file patent applications covering certain of our inventions;
- others may independently develop the same, similar, or alternative technologies without infringing, misappropriating or violating our intellectual property rights;
- it is possible that our pending patent applications will not lead to issued patents;

- issued patents may not provide us with any competitive advantages, or may be narrowed or held invalid or unenforceable, including as a result of legal challenges;

- our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for certain research and development activities, as well as in countries where we do not have patent rights, and may then use the information learned from such activities to develop competitive products for sale in our major commercial markets;

- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such trade secrets or know-how; and

- the patents of others may have an adverse effect on our business.

Should any of these events occur, they could have a material adverse impact on our business and financial condition.

Risks Related to Ownership of our Common Stock

Our stock price has been and will likely continue to be volatile and may decline regardless of our operating performance. Volatility in our share price could subject us to securities class action litigation.

Our stock price has fluctuated in the past and is likely to be volatile in the future. From January 1, 2022 through December 31, 2022, the reported sale price of our common stock has fluctuated between $6.91 and $37.05 per share. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may experience losses on their investment in our common stock, including due to the factors discussed in these "Risk Factors" and elsewhere in this Annual Report.

In addition, securities class action litigations have often been brought against companies following a decline in the market price of their securities. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

We are required to develop and maintain proper and effective internal controls over financial reporting and any failure to maintain the adequacy of these internal controls may adversely affect investor confidence in our company and, as a result, the value of our common stock.

We are required, pursuant to Section 404 of the Sarbanes-Oxley Act (Section 404), to furnish a report by management on the effectiveness of our internal control over financial reporting. This assessment needs to include disclosure of any material weaknesses identified by our management in our internal control over financial reporting. If we have a material weakness and our independent registered public accounting firm is required to attest to the effectiveness of our internal control over financial reporting, we would receive an adverse opinion.

We currently do not have an internal audit group, and we may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge and continue the costly and challenging process of compiling the system and processing documentation necessary to perform the evaluation needed to comply with Section 404. We may not complete our continued evaluation, testing and any required remediation in a timely fashion. During our evaluation of our internal control, if we identify one or more material weaknesses in our internal control over financial reporting or fail to remediate any material weaknesses, we will be unable to assert that our internal control over financial reporting is effective. Any material weakness or other failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition or results of operations.

Our certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation ("Certificate of Incorporation") provides that the Court of Chancery of the State of Delaware will be the exclusive forum for certain actions and proceedings. Furthermore, Section 22 of the Securities Act of 1933, as amended, creates concurrent jurisdiction for federal and state courts over all Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. The choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes, which may discourage such lawsuits. Alternatively, if a court were to find the choice of forum provision contained in our Certificate of Incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions.

Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, even if an acquisition would be beneficial to our stockholders and may prevent attempts by our stockholders to replace or remove our current management.

There are provisions in our Certificate of Incorporation and Bylaws, such as the existence of a classified board and the authorization of "blank-check" preferred stock, that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by our stockholders. 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, who are responsible for appointing the members of our management.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibit a person who owns 15% or more 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. Any provision in our Certificate of Incorporation, our Bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock and could also affect the price that some investors are willing to pay for our common stock.

General Risk Factors

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

Our ability to use our federal and state net operating losses ("NOLs") to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income, and we cannot predict with certainty when, or whether, we will generate sufficient taxable income to use our NOLs. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire.

Under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, if a corporation undergoes an "ownership change", generally defined as a greater than fifty percentage point change (by value) in its equity ownership by certain stockholders over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards, or NOLs, and other pre-change tax attributes (such as research and development tax credits) to offset its post-change taxable income or tax liability may be limited. We have experienced ownership changes in the past, resulting in annual limitations in our ability to use our NOLs and credits. In addition, we may experience subsequent ownership changes as a result of future equity offerings or other changes in the ownership of our stock, some of which are beyond our control. As a result, the amount of the NOLs and tax credit carryforwards presented in our financial statements could be limited and may expire unused. Any such material limitation or expiration of our NOLs may harm our future operating results by effectively increasing our future tax obligations.

We may have additional tax liabilities.

We are regularly subject to audits by tax authorities in the jurisdictions in which we conduct business. Although we believe our tax positions are reasonable, the final outcome of tax audits and related litigation could be materially different than that reflected in our historical income tax provisions and accruals, and we could be subject to assessments of additional taxes and/or substantial fines or penalties. The resolution of any audits or litigation could have an adverse effect on our financial position and results of operations. We and our subsidiary are engaged in intercompany transactions, the terms and conditions of which may be scrutinized by tax authorities, which could result in additional tax and/or penalties becoming due.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We lease approximately 57,900 square feet of office and laboratory space in Newark, California under a lease agreement, as amended, that expires in May 2024. We believe that our existing facilities are adequate to meet our current business needs. We anticipate that additional space will be available on commercially reasonable terms, if required.

Item 3. Legal Proceedings

From time to time, we may become subject to litigation and claims arising in the ordinary course of business. We are not currently a party to any material legal proceedings and we are not currently aware of any pending or threatened legal proceeding against us that we believe could have a material adverse effect on our business, operating results, financial condition or cash flows. Refer to Note 11 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information on our historical legal proceedings.

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 trades on The Nasdaq Stock Market, LLC under the symbol "PTGX."

Stockholders

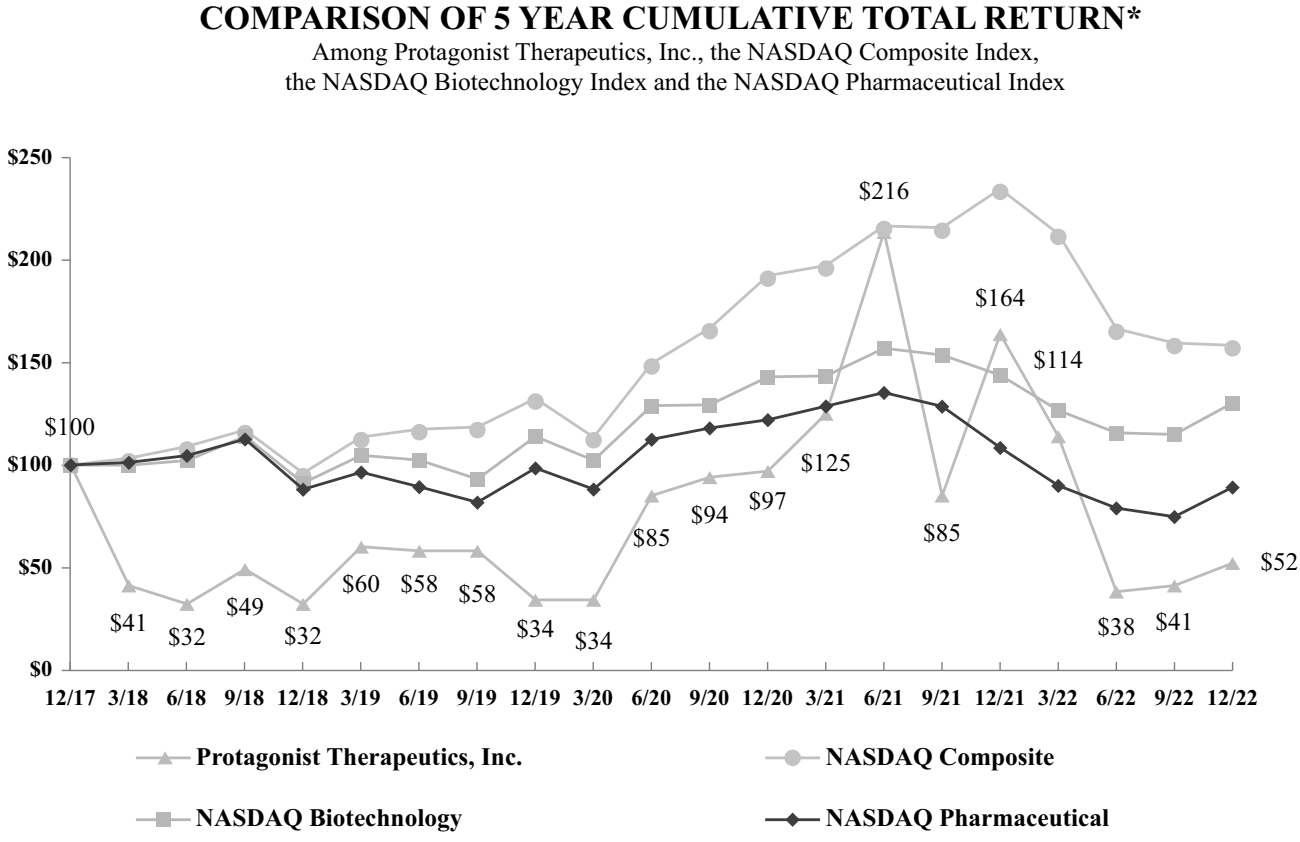
As of the close of business on March 2, 2023, there were two stockholders of record of our common stock. The number of stockholders of record is based upon the actual number of stockholders registered at such date and does not include holders of shares in "street names" or persons, partnerships, associates, or corporations, or other entities identified in security listings maintained by depositories.

Dividends

We have never declared or paid any cash dividends. We currently expect to retain all future earnings, if any, for use in the operation and expansion of our business, and therefore do not anticipate paying any cash dividends in the foreseeable future.

Performance Graph

The following is not deemed "filed" with the Securities and Exchange Commission and shall not be incorporated by reference into any filing we make under the Securities and Exchange Act of 1934, as amended, or the Securities Act of 1933, as amended, whether made before or after the date hereof and irrespective of any general incorporation by reference language in such filing. The graph below shows the cumulative total stockholder return assuming an investment on December 31, 2017 in each of our common stock, the Nasdaq Composite Index, the Nasdaq Biotechnology Index, and the Nasdaq Pharmaceutical Index. The graph compares the performance of a $100 investment in our common stock and in each index (assuming reinvestment of all dividends) from December 31, 2017 to December 31, 2022.



**The comparisons in the graph are based on historical data and are not indicative of, or intended to forecast, future performance of our common stock.*

Sale of Unregistered Securities

None.

Issuer Purchases of Equity Securities

None.

Item 6. Reserved

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

Overview

We are a biopharmaceutical company with peptide-based new chemical entities rusfertide and JNJ-2113 (formerly known as PN-235) in different stages of development, all derived from our proprietary discovery technology platform. Our clinical programs fall into two broad categories of diseases; (i) hematology and blood disorders, and (ii) inflammatory and immunomodulatory diseases.

Rusfertide

Our most advanced clinical asset, rusfertide (generic name for PTG-300), is an injectable hepcidin mimetic in development for the potential treatment of erythrocytosis, iron overload and other blood disorders and is wholly owned. Hepcidin is a key hormone in regulating iron equilibrium and is critical to the proper development of red blood cells. Rusfertide mimics the effect of the natural hormone hepcidin, but with greater potency, solubility and stability. Data from our rusfertide Phase 2 clinical trials presented at medical conferences in 2021 and 2022 provided evidence regarding the potential of rusfertide for managing hematocrit, reducing thrombotic risk and improving iron deficiency symptoms. Rusfertide has a unique mechanism of action in the potential treatment of the blood disorder polycythemia vera ("PV"), which may enable it to specifically decrease and maintain hematocrit levels within the range of recommended clinical guidelines without causing the iron deficiency that can occur with frequent phlebotomy. Our rusfertide Phase 2 clinical trials include the following:

- REVIVE, a Phase 2 proof of concept ("POC") trial, was initiated in the fourth quarter of 2019. We completed enrollment of patients in the first quarter of 2022 with a target of approximately 50 patients to be enrolled through the end of the randomization portion of the trial, which was completed during the first quarter of 2023, and will continue in open label extension.

- PACIFIC, another Phase 2 trial for rusfertide patients diagnosed with PV and with routinely elevated hematocrit levels (>48%), was initiated during the first quarter of 2021 and completion of the 52-week trial is expected during the second quarter of 2023.

At the June 2022 American Society of Clinical Oncology ("ASCO") Annual Meeting, we presented updated interim results for REVIVE and PACIFIC demonstrating the effects of dosing interruption and resumption. Rusfertide dosing interruption led to loss of effect, including increased phlebotomy rate and increases in hematocrit and red blood cells. Rusfertide restart restored therapeutic benefits. Following the brief clinical hold described below, over 90% of patients in the REVIVE trial provided reconsent and returned to rusfertide treatment after dosing interruption and reinitiation. At the June 2022 European Hematology Association Congress, we presented interim data as of May 2022 showing that rusfertide treatment interruption reverses hematologic gains and re-initiation of treatment restores therapeutic benefits in patients with PV. At the December 2022 American Society of Hematology meeting, we presented data as of October 2022 related to rusfertide, including a subgroup of analyses of the adverse event profile from the REVIVE trial. These preliminary results indicated that 84% of treatment-emergent adverse events ("TEAEs") were Grade 2 or below. 16% of patients experienced Grade 3 TEAEs and there were no Grade 4 TEAEs.

On March 15, 2023, we announced positive topline results from the blinded, placebo-controlled, randomized withdrawal portion of the REVIVE trial. Subjects receiving rusfertide achieved statistically significant improvements versus placebo in the trial's primary endpoint.

The double-blind, placebo-controlled, 12-week randomized withdrawal portion was included as Part 2 of the REVIVE trial study to evaluate rusfertide in PV patients with frequent phlebotomy requirements. In the REVIVE trial, subjects were initially enrolled in the 28-week open label dose-titration and efficacy evaluation Part 1 of the study, followed by 1:1 randomization of 53 subjects to placebo versus rusfertide therapy for a subsequent duration of 12 weeks.

More subjects receiving rusfertide during the blinded randomized withdrawal portion of the REVIVE trial were responders compared with placebo (69.2% versus 18.5%, p=0.0003). A study subject was defined as a responder if the subject completed 12 weeks of double-blind treatment while maintaining hematocrit control without phlebotomy eligibility and without phlebotomy. During the 12 weeks of the blinded randomized withdrawal, only 2 of 26 subjects on rusfertide were phlebotomized.

VERIFY, a global Phase 3 clinical trial of rusfertide in PV for approximately 250 patients, was initiated in the first quarter of 2022. Significant efforts have been taken toward the goal of full enrollment and a high degree of interest has been observed from physicians and patient communities. We expect enrollment completion in the fourth quarter of 2023.

On September 16, 2021, the U.S. Food and Drug Administration ("FDA") placed a clinical hold on our then ongoing rusfertide clinical trials following our submission to the FDA of findings in a 26-week rasH2 transgenic mouse carcinogenicity study. In October 2021, we submitted a Complete Response to the FDA related to the clinical hold, and the FDA removed the clinical hold on October 8, 2021. In our Complete Response, we provided the individual patient clinical safety reports the FDA requested for human cancers observed in rusfertide clinical trials, updated the investigator brochure and patient informed consent forms for ongoing rusfertide trials, proposed new safety and stopping rules in trial protocols for our ongoing rusfertide clinical trials, and performed a comprehensive review of our rusfertide safety database. Dosing of patients and enrollment in ongoing clinical trials with rusfertide resumed in the fourth quarter of 2021.

The FDA granted orphan drug designation for rusfertide for the treatment of PV in June 2020, and Fast Track designation for rusfertide for the treatment of PV in December 2020. The EMA granted orphan drug designation for rusfertide for treatment of PV in October 2020. The FDA granted Breakthrough Therapy Designation for rusfertide for the treatment of PV in June 2021. In April 2022, we received a letter from the FDA indicating the FDA's intent to rescind Breakthrough Therapy Designation for rusfertide in PV. In June 2022, we voluntarily withdrew our Breakthrough Therapy Designation following correspondence with FDA and based on our internal analysis of the relative utility of Breakthrough Therapy Designation for Phase 3 trials and beyond. The FDA correspondence relating to the Breakthrough Therapy designation does not address the rusfertide Fast Track Designation, which remains active.

In keeping with our organizational prioritization of rusfertide in PV, plans to initiate trials of rusfertide in additional disease indications have been paused. This decision was influenced in part by the enactment of the Inflation Reduction Act ("IRA") in the United States and includes previously planned trials of rusfertide in the subset of hereditary hemochromatosis patients with chronic arthropathy.

JNJ-2113 (formerly known as PN-235)

Our partnered Interleukin-23 receptor ("IL-23R") antagonist compound JNJ-2113 is an orally delivered investigational drug that is designed to block biological pathways currently targeted by marketed injectable antibody drugs. Our orally stable peptide approach may offer a targeted therapeutic approach for gastrointestinal ("GI") and systemic compartments as needed. We believe that, compared to antibody drugs, JNJ-2113 has the potential to provide clinical improvement in an oral medication with increased convenience and compliance and the opportunity for the earlier introduction of targeted oral therapy.

In May 2017, we entered into a worldwide license and collaboration agreement with Janssen Biotech, Inc. ("Janssen"), a Johnson & Johnson company, to co-develop and co-detail our IL-23R antagonist compounds, including PTG-200 (JNJ-67864238) and certain related compounds for all indications, including inflammatory bowel disease ("IBD"). PTG-200 was a first-generation investigational, orally delivered, IL-23R antagonist for the treatment of IBD. The agreement with Janssen was amended in May 2019 to expand the collaboration by supporting efforts towards second-generation IL-23R antagonists; and in July 2021 to, among other things, enable Janssen to independently research and develop collaboration compounds for multiple indications in the IL-23 pathway and further align our financial interests.

During the fourth quarter of 2021, following a pre-specified interim analysis criteria, a portfolio decision was made by Janssen to advance second-generation product candidate JNJ-2113 (JNJ-77242113) based on its superior potency and overall pharmacokinetic and pharmacodynamic profile. A JNJ-2113 Phase 1 trial was completed in the fourth quarter of 2021.

In February 2022, Janssen initiated FRONTIER1, a 255-patient Phase 2b clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis, which was completed in December 2022. FRONTIER1 was a randomized, multicenter, double-blind, placebo-controlled study that evaluated three once-daily dosages and two twice-daily dosages of JNJ-2113 taken orally. The primary endpoint of the study is the proportion of patients achieving PASI-75 (a 75% improvement in skin lesions as measured by the Psoriasis Area and Severity Index) at 16 weeks. In March 2023, we announced positive topline results from the trial. JNJ-2113 achieved the study's primary efficacy endpoint, with a statistically significant greater proportion of patients who received JNJ-2113 achieving PASI-75 responses compared to placebo at Week 16 in all five of the study's treatment groups. A clear dose response was observed across an eight-fold dose range. Treatment was well tolerated, with no meaningful difference in frequency of adverse events across treatment groups versus placebo. It is our expectation that JNJ-2113 will progress into a Phase 3 registrational study in plaque psoriasis on the strength of the FRONTIER1 data. Advancement of JNJ-2113 into a Phase 3 study and meeting the primary endpoint in that study would qualify us for milestone payments of $50 million and $115 million, respectively. Data will be presented from various pre-clinical and clinical studies on JNJ-2113 at medical conferences beginning in the second quarter of 2023.

Other Phase 2 studies of JNJ-2113 that Janssen has initiated include the SUMMIT study of JNJ-2113 for the treatment of moderate-to-severe plaque psoriasis expected to be completed in the second quarter of 2023 and FRONTIER2, a long-term extension study. A Phase 1 trial of an immediate release formulation of JNJ-2113 in healthy Japanese and Chinese adult participants is currently recruiting. Following the completion of Phase 2 studies of JNJ-2113 in plaque psoriasis, we expect Janssen to initiate a separate Phase 2 trial of JNJ-2113 in a second indication. Additional indications may include any or all of psoriatic arthritis, UC and CD.

During the fourth quarter of 2021, we received a $7.5 million milestone payment from Janssen triggered by the completion of data collection for JNJ-2113 Phase 1 activities. In the second quarter of 2022, we received a $25.0 million milestone payment in connection with the dosing of a third patient in FRONTIER1 during the first quarter of 2022. We will be eligible to receive a $10.0 million milestone payment in connection with the dosing of a third patient in the second Phase 2 trial of a second-generation candidate, a $50 million milestone upon dosing of a third patient in a Phase 3 trial for a second-generation compound for any indication, and a $115.0 million milestone payment upon a Phase 3 clinical trial for a second-generation compound for any indication meeting its primary clinical endpoint. We remain eligible for up to approximately $855.0 million in future development and sales milestone payments, in addition to the $112.5 million in nonrefundable payments from Janssen received to date. We also remain eligible to receive tiered royalties on net product sales at percentages ranging from mid-single digits to ten percent.

PN-943

PN-943 is a wholly owned, investigational, orally delivered, gut-restricted alpha 4 beta 7 ("α4β7") specific integrin antagonist for IBD. During the second quarter of 2020, we initiated IDEAL, a 159 patient Phase 2 trial evaluating the safety, tolerability and efficacy of PN-943 in patients with moderate to severe UC. Enrollment in IDEAL was completed during the first quarter of 2022. The trial includes a 12-week induction period, which has been completed, and a 40-week extended treatment period. With the exception of completing the 40-week extended treatment period for eligible patients in the IDEAL trial, which is expected to be completed in the first quarter of 2023, we do not intend to dedicate further internal resources to clinical development or contract manufacturing activities for our PN-943 clinical program.

Discovery Platform

Our clinical assets are all derived from our proprietary discovery platform. Our platform enables us to engineer novel, structurally constrained peptides that are designed to retain key advantages of both orally delivered small molecules and injectable antibody drugs in an effort to overcome many of their limitations as therapeutic agents.

Importantly, constrained peptides can be designed to potentially alleviate the fundamental instability inherent in traditional peptides to allow different delivery forms, such as oral, subcutaneous, intravenous, and rectal. We continue to use our peptide technology platform to discover product candidates against targets in disease areas with significant unmet medical needs. For example, we have a pre-clinical stage program to identify an orally active hepcidin mimetic, which we believe will be complementary to the injectable rusfertide for offering the best treatment options for PV, hereditary hemochromatosis and other potential erythropoietic and iron imbalance disorders.

Business Outlook

We are subject to risks and uncertainties as a result of the prolonged nature of the COVID-19 pandemic and emergent variants with increased transmissibility, even in those who are fully vaccinated. Some of the workforce trends starting during the pandemic have continued to lead to staffing shortages in settings such as clinical trial sites and healthcare offices. The future impact of COVID-19 on our activities will depend on a number of factors, including, but not limited to, the scope and magnitude of any resurgences in the outbreak and the spread of COVID-19 variants; the timing, extent, effectiveness and durability of COVID-19 vaccine programs or other treatments; and new travel and other restrictions and public health measures. We have experienced delays in our existing and planned clinical trials due to the worldwide impacts of the pandemic. Our future results of operations and liquidity could be adversely impacted by further delays in existing and planned clinical trials, continued difficulty in recruiting patients for these clinical trials, delays in manufacturing and collaboration activities, supply chain disruptions and the ongoing impact on our operating activities and employees. In addition, a recession or market correction related to or amplified by COVID-19 could materially affect our business.

We are currently operating in a period of economic uncertainty and capital markets disruption, which has been impacted by domestic and global monetary and fiscal policy, geopolitical instability, the ongoing military conflict between Russia and Ukraine and the rising tensions between China and Taiwan, a recessionary environment and historically high domestic and global inflation. In particular, the conflict in Ukraine has exacerbated market disruptions, including significant volatility in commodity prices, as well as supply chain interruptions, and has contributed to record inflation globally. The U.S. Federal Reserve and other central banks may be unable to contain inflation through more restrictive monetary policy and inflation may increase or continue for a prolonged period of time. Inflationary factors, such as increases in the cost of clinical supplies, interest rates, overhead costs and transportation costs may adversely affect our operating results. Also, the failure of Silicon Valley Bank and other banks in the United States in March 2023 has given rise to uncertainty in the security of amounts in deposit accounts uninsured by the Federal Deposit Insurance Corporation. We continue to monitor these events and the potential impact on our business. Although we do not believe that inflation has had a material impact on our financial position or results of operations to date, we may be adversely affected in the future due to domestic and global monetary and fiscal policy, supply chain constraints, consequences associated with COVID-19 and the ongoing conflict between Russia and Ukraine, and such factors may lead to increases in the cost of manufacturing our product candidates and delays in initiating trials.

Operations

We have incurred net losses in each year since inception and we do not anticipate achieving sustained profitability in the foreseeable future. Our net losses were $127.4 million, $125.6 million and $66.2 million for the years ended December 31, 2022, 2021 and 2020, respectively. As of December 31, 2022, we had an accumulated deficit of $536.8 million. Substantially all of our net losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to continue to incur significant research and development expenses and other expenses related to our ongoing operations, product development, and pre-commercialization activities. As a result, we expect to continue to incur losses in the future as we continue our development of, and seek regulatory approval for, our product candidates.

Janssen License and Collaboration Agreement

On July 27, 2021, we entered into the Restated Agreement with Janssen, which amends and restates the Original Agreement, as amended by the First Amendment. Janssen is a related party to us as Johnson & Johnson Innovation—JJDC, Inc., a significant stockholder of ours, and Janssen are both subsidiaries of Johnson & Johnson. Upon the effectiveness of the Original Agreement, we received a non-refundable, upfront cash payment of $50.0 million from Janssen. Upon the effectiveness of the First Amendment, we received a $25.0 million payment from Janssen in 2019. In the first quarter of 2020, we received a $5.0 million payment triggered by the successful nomination of a second-generation IL-23R antagonist development compound. In the fourth quarter of 2021, we received a $7.5 million milestone payment from Janssen triggered by completion of the data collection for JNJ-2113 Phase 1 activities. In the second quarter of 2022, we received a $25.0 million milestone payment in connection with the dosing of a third patient in FRONTIER1 during the first quarter of 2022. See Note 3 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Critical Accounting Polices and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with United States generally accepted accounting principles. 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 liabilities at the date of the consolidated financial statements, as well as the reported revenue generated, and the expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, and 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. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Use of Estimates

The preparation of the consolidated financial statements in conformity with GAAP requires management to make estimates, assumptions and judgments that affect the reported amounts of assets and liabilities and disclosure of contingent liabilities as of the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. On an ongoing basis, we evaluate our estimates, including those related to revenue recognition, accruals for research and development activities, stock-based compensation, income taxes, marketable securities and leases. Estimates related to revenue recognition include actual costs incurred versus total estimated costs of our deliverables to determine percentage of completion in addition to the application and estimates of potential revenue constraints in the determination of the transaction price under its license and collaboration agreements. We base these estimates on historical and anticipated results, trends and various other assumptions that we believe are reasonable under the circumstances, including assumptions as to forecasted amounts and future events.

Due to the COVID-19 pandemic, military conflict between Ukraine and Russia, rising tensions between China and Taiwan and inflationary pressures, among other factors, there has been uncertainty and disruption in the global economy and financial markets. We have taken into consideration any known impacts in our accounting estimates to date and are not aware of any additional specific events or circumstances that would require any additional updates to our estimates or judgments or a revision of the carrying value of our assets or liabilities as of the date of the filing of this Annual Report on Form 10-K. These estimates may change as new events occur and additional information is obtained. Actual results could differ materially from these estimates under different assumptions or conditions.

Revenue Recognition

Under Accounting Standards Codification Topic 606, Revenue from Contracts with Customers ("ASC 606"), we recognize revenue when our customer obtains control of promised goods or services, in an amount that reflects the

consideration which we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that we determine are 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 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. At contract inception, we assess the goods or services promised within each contract, determine those that are performance obligations, and assess whether each promised good or service is distinct. We then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligations when (or as) the performance obligations are satisfied. We constrain our estimate of the transaction price up to the amount (the "variable consideration constraint") that a significant reversal of recognized revenue is not probable.

Licenses of intellectual property: If a license to our intellectual property is determined to be distinct from the other performance obligations identified in an arrangement, we recognize revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are bundled with other promises, we utilize judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring proportional performance for purposes of recognizing revenue from non-refundable, upfront fees. We evaluate the measure of proportional performance each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement or amendment that includes development, regulatory or commercial milestone payments, we evaluate whether the milestones are considered probable of being reached and estimate the amount to be included in the transaction price. ASC 606 suggests two alternatives to use when estimating the amount of variable consideration: the expected value method and the most likely amount method. Under the expected value method, an entity considers the sum of probability-weighted amounts in a range of possible consideration amounts. Under the most likely amount method, an entity considers the single most likely amount in a range of possible consideration amounts. Whichever method is used should be consistently applied throughout the life of the contract; however, it is not necessary for us to use the same approach for all contracts. We expect to use the most likely amount method for development and regulatory milestone payments. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within our control or the control of the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. If there is more than one performance obligation, the transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis. We recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, we re-evaluate the probability or achievement of each such milestone and any related constraint, and if necessary, adjust our estimates of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Any potential milestone payments that we determine are not associated with performance obligations as defined under the contract are excluded from the transaction price and are recognized as the triggering event occurs.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, where the license is deemed to be the predominant item to which the royalties relate, we recognize revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Upfront payments and fees are recorded as deferred revenue upon receipt or when due and may require deferral of revenue recognition to a future period until we perform our obligations under these arrangements. Amounts payable to us are recorded as accounts receivable when our right to consideration is unconditional. Amounts payable to us and not yet billed to the collaboration partner are recorded as contract assets. We do not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less.

Contractual cost sharing payments made to a customer or collaboration partner are accounted for as a reduction to the transaction price if such payments are not related to distinct goods or services received from the customer or collaboration partner.

Contracts may be amended to account for changes in contract specifications and requirements. Contract modifications exist when the amendment either creates new, or changes existing, enforceable rights and obligations. When contract modifications create new performance obligations and the increase in consideration approximates the standalone selling price for goods and services related to such new performance obligations, as adjusted for specific facts and circumstances of the contract, the modification is considered to be a separate contract and revenue is recognized prospectively. If a contract modification is not accounted for as a separate contract, we account for the promised goods or services not yet transferred at the date of the contract modification (the remaining promised goods or services) prospectively, as if it were a termination of the existing contract and the creation of a new contract, if the remaining goods or services are distinct from the goods or services transferred on or before the date of the contract modification. We account for a contract modification as if it were a part of the existing contract if the remaining goods or services are not distinct and, therefore, form part of a single performance obligation that is partially satisfied at the date of the contract modification. In such case the effect that the contract modification has on the transaction price, and on the entity's measure of progress toward complete satisfaction of the performance obligation, is recognized as an adjustment to revenue (either as an increase in or a reduction of revenue) at the date of the contract modification (the adjustment to revenue is made on a cumulative catch-up basis).

Research and Development Costs

Research and development costs are expensed as incurred, unless there is an alternate future use in other research and development projects or otherwise. Research and development costs include salaries and benefits, stock-based compensation expense, laboratory supplies and facility-related overhead, outside contracted services, including clinical trial costs, manufacturing and process development costs for both clinical and pre-clinical materials, research costs, development milestone payments under license and collaboration agreements, and other consulting services.

We accrue for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of pre-clinical studies and clinical trials, and contract manufacturing activities. We record the estimated costs of research and development activities based upon the estimated services provided but not yet invoiced and we include these costs in accrued expenses and other payables in our consolidated balance sheets and within research and development expense in our consolidated statements of operations. We accrue for these costs based on various factors such as estimates of the work completed and in accordance with agreements established with our third-party service providers. As actual costs become known, we adjust our accrued liabilities. We have not experienced any material differences between accrued liabilities and actual costs incurred. However, the status and timing of actual services performed, number of patients enrolled, the rate of patient enrollment and the number and location of sites activated may vary from our estimates and may result in adjustments to our research and development expenses in future periods. Changes in these estimates that result in material changes to our accruals could materially affect our results of operations.

Recent Accounting Pronouncements

Information regarding recent accounting pronouncements applicable to us is included in Note 2 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K.

Components of Our Results of Operations

License and Collaboration Revenue

Our license and collaboration revenue is derived from payments we receive under the Janssen License and Collaboration Agreement. See Note 3 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Research and Development Expenses

Research and development expenses represent costs incurred to conduct research, such as the discovery and development of our product candidates. We recognize all research and development costs as they are incurred unless there is an alternative future use in other research and development projects or otherwise. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received, rather than when payment has been made. In instances where we enter into agreements with third parties to provide research and development services to us, costs are expensed as services are performed. Amounts due under such arrangements may be either fixed fee or fee for service and may include upfront payments, monthly payments, and payments upon the completion of milestones or the receipt of deliverables.

Research and development expenses consist primarily of the following:

- expenses incurred under agreements with clinical study sites that conduct research and development activities on our behalf;
- employee-related expenses, which include salaries, benefits and stock-based compensation;
- laboratory vendor expenses related to the preparation and conduct of pre-clinical, non-clinical, and clinical studies;
- costs related to production of clinical supplies and non-clinical materials, including fees paid to contract manufacturers;
- license fees and milestone payments under license and collaboration agreements; and
- facilities and other allocated expenses, which include expenses for rent and maintenance of facilities, information technology, depreciation and amortization expense and other supplies.

We recognize the amounts related to our Australian research and development refundable cash tax incentive that are not subject to refund provisions as a reduction of research and development expenses. The research and development tax incentives are recognized when there is reasonable assurance that the incentives will be received, the relevant expenditure has been incurred and the amount of the consideration can be reliably measured. We evaluate our eligibility under the tax incentive program as of each balance sheet date and make accruals and related adjustments based on the most current and relevant data available. We may alternatively be eligible for a taxable credit in the form of a non-cash tax incentive. We recognize the amounts from grants under government programs as a reduction of research and development expenses when the related research costs are incurred.

We allocate direct and indirect costs incurred to product candidates when they enter clinical development. For product candidates in clinical development, direct costs consist primarily of clinical, pre-clinical, and drug discovery costs, costs of supplying drug substance and drug product for use in clinical and pre-clinical studies, including clinical manufacturing costs, contract research organization fees, and other contracted services pertaining to specific clinical and pre-clinical studies. Indirect costs allocated to our product candidates on a program-specific basis include research and development employee salaries, benefits, and stock-based compensation, and indirect overhead and other administrative support costs. Program-specific costs are unallocated when the clinical expenses are incurred for our early-stage research and drug discovery projects as our internal resources, employees and infrastructure are not tied to any one research or drug discovery project and are typically deployed across multiple projects. As such, we do not provide financial information regarding the costs incurred for early stage pre-clinical and drug discovery programs on a program-specific basis prior to the clinical development stage.

We expect our research and development expenses to decrease in the near term as we continue to de-prioritize our PN-943 clinical program and streamline certain discovery programs to focus our resources toward progressing our rusfertide program into later stage clinical trials and preparing for commercialization. The process of conducting research, identifying potential product candidates and conducting pre-clinical and clinical trials necessary to obtain regulatory approval and commencing pre-commercialization activities is costly and time intensive. We may never succeed in achieving marketing approval for our product candidates regardless of our costs and efforts. The probability of success of our product candidates may be affected by numerous factors, including pre-clinical data, clinical data, competition, manufacturing capability, our cost of goods to be sold, our ability to receive, and the timing of, regulatory approvals, market conditions, and our ability to successfully commercialize our products if they are approved for marketing. As a result, we are unable to determine the duration and completion costs of our research and development projects or when and to what extent we will generate revenue from the commercialization and sale of any of our product candidates. Our research and development programs are subject to change from time to time as we evaluate our priorities and available resources. With the exception of completing the 40-week extended treatment period for eligible patients in the Phase 2 IDEAL trial, which we expect to be completed in the first quarter of 2023, we do not intend to dedicate further internal resources to clinical development or contract manufacturing activities for our PN-943 clinical program. We will continue to explore out-licensing opportunities globally.

General and Administrative Expenses

General and administrative expenses consist of personnel costs, allocated facilities costs and other expenses for outside professional services, including legal, human resources, audit and accounting services, and pre-commercialization expenses, including selling and marketing costs. Personnel costs consist of salaries, benefits and stock-based compensation. Allocated expenses consist of expenses for rent and maintenance of facilities, information technology, depreciation and amortization expense and other administrative supplies. We expect to continue to incur expenses supporting our continued operations as a public company, including expenses related to compliance with the rules and regulations of the SEC and those of the national securities exchange on which our securities are traded, insurance expenses, investor relations expenses, audit fees, professional services and general overhead and administrative costs.

Interest Income

Interest income consists of interest earned on our cash, cash equivalents, and marketable securities, which is comprised of contractual interest, premium amortization and discount accretion.

Interest Expense

Interest expense consists of interest recognized on our long-term debt, which is comprised of contractual interest, amortization of origination fees and other issuance costs, and accretion of final payment fees.

Loss on Early Repayment of Debt

Loss on early repayment of debt consists of prepayment and final payment fees paid upon the early repayment of our long-term debt.

Other Expense, Net

Other expense, net consists primarily of amounts related to foreign exchange gains and losses and related items.

Results of Operations

	Year Ended December 31, 2022	Year Ended December 31, 2021	Dollar Change	% Change
	(Dollars in thousands)			
License and collaboration revenue—related party	$ 26,581	$ 27,357	$ (776)	(3)
Operating expenses:				
Research and development [1]	126,215	126,006	209	—
General and administrative [2]	31,739	27,196	4,543	17
Total operating expenses	157,954	153,202	4,752	3
Loss from operations	(131,373)	(125,845)	(5,528)	4
Interest income	4,060	443	3,617	*
Other expense, net	(80)	(149)	69	(46)
Net loss	$ (127,393)	$ (125,551)	$ (1,842)	1

[1] Includes $14.7 million and $9.0 million of non-cash stock-based compensation expense for the years ended December 31, 2022 and 2021, respectively.

[2] Includes $9.5 million and $7.4 million of non-cash stock-based compensation expense for the years ended December 31, 2022 and 2021, respectively.

*Percentage not meaningful

License and Collaboration Revenue

License and collaboration revenue decreased $0.8 million, or 3%, from $27.4 million for the year ended December 31, 2021 to $26.6 million for the year ended December 31, 2022. The decrease in revenue was primarily due to a decrease in services under the Janssen License and Collaboration Agreement recognized based on proportional performance. We completed our performance obligation pursuant to the collaboration as of June 30, 2022.

We determined that the final transaction price of the initial performance obligation under the Restated Agreement is $131.7 million as of December 31, 2022, an increase of $25.2 million from the transaction price of $106.5 million as of December 31, 2021. In order to determine the transaction price, we evaluated all payments to be received during the duration of the contract, net of development costs reimbursement expected to be payable to Janssen. The transaction price as of December 31, 2022 includes $112.5 million of nonrefundable payments received as of June 30, 2022, $17.9 million of reimbursement from Janssen for services performed for IL-23 receptor antagonist compound research and other services, and variable consideration consisting of $8.2 million of development cost reimbursement from Janssen, partially offset by $6.9 million of net cost reimbursement due to Janssen for services performed.

Research and Development Expenses

	Year Ended December 31, 2022	Year Ended December 31, 2021	Dollar Change	% Change
	(Dollars in thousands)			
Clinical and development expense—rusfertide (PTG-300)	$ 64,789	$ 55,382	$ 9,407	17
Clinical and development expense—PN-943	36,906	37,655	(749)	(2)
Clinical and development expense—JNJ-2113 (PN-235)	201	4,777	(4,576)	(96)
Clinical and development expense—PN-232	356	2,037	(1,681)	(83)
Clinical and development expense—PTG-200	53	23	30	130
Clinical and development expense—PTG-100	248	374	(126)	(34)
Preclinical and drug discovery research expense	23,704	24,943	(1,239)	(5)
Milestone payment obligation to former collaboration partner	—	4,000	(4,000)	(100)
Grants and tax incentives expense reimbursement, net	(42)	(3,185)	3,143	(99)
Total research and development expenses	$ 126,215	$ 126,006	$ 209	—

We had 82 and 92 full-time equivalent research and development employees as of December 31, 2022 and 2021, respectively. Research and development expenses for the year ended December 31, 2022 included increases of $5.7 million in stock-based compensation expense and $4.7 million of other personnel-related expenses compared to the year ended December 31, 2021.

General and Administrative Expenses

General and administrative expenses increased $4.5 million, or 17%, from $27.2 million for the year ended December 31, 2021 to $31.7 million for the year ended December 31, 2022, primarily due to increases of $2.2 million in personnel-related expenses and $2.3 million in other expenses to support the growth of our business. The increase in personnel-related expenses was primarily due to an increase of $2.1 million in stock-based compensation expense.

We had 23 and 26 full-time equivalent general and administrative employees as of December 31, 2022 and 2021, respectively.

Interest Income

Interest income increased $3.6 million, from $0.4 million for the year ended December 31, 2021 to $4.1 million for the year ended December 31, 2022. This increase was primarily due to higher yields on invested balances during a period of increasing interest rates compared to the prior year period.

Comparison of the Years Ended December 31, 2021 and 2020

	Year Ended December 31,		Dollar	%
	2021	2020	Change	Change
	(Dollars in thousands)			
License and collaboration revenue—related party	$ 27,357	$ 28,628	$ (1,271)	(4)
Operating expenses:				
Research and development [1]	126,006	74,506	51,500	69
General and administrative [2]	27,196	18,638	8,558	46
Total operating expenses	153,202	93,144	60,058	64
Loss from operations	(125,845)	(64,516)	(61,329)	95
Interest income	443	900	(457)	(51)
Interest expense	—	(598)	598	(100)
Loss on early repayment of debt	—	(585)	585	(100)
Other expense, net	(149)	(46)	(103)	224
Loss before income tax expense	(125,551)	(64,845)	(60,706)	94
Income tax expense	—	(1,305)	1,305	(100)
Net loss	$ (125,551)	$ (66,150)	$ (59,401)	90

[1] Includes $9.0 million and $4.1 million of non-cash stock-based compensation expense for the years ended December 31, 2021 and 2020, respectively.

[2] Includes $7.4 million and $3.8 million of non-cash stock-based compensation expense for the years ended December 31, 2021 and 2020, respectively.

License and Collaboration Revenue

License and collaboration revenue decreased $1.3 million, or 4%, from $28.6 million for the year ended December 31, 2020 to $27.4 million for the year ended December 31, 2021. The decrease in license and collaboration revenue was primarily related to a decrease in services provided under the Janssen License and Collaboration Agreement recognized based on proportional performance, partially offset by an $8.0 million cumulative catch-up amount recognized during the year ended December 31, 2021. This cumulative catch-up was primarily the result of an

acceleration of our cumulative performance completed, following the execution of the Restated Agreement, which reduced our remaining performance obligation. Revenue for the year ended December 31, 2020 included an update in the amounts forecasted for future services remaining to be performed under the Janssen License and Collaboration Agreement which correspondingly increased our overall cumulative percentage of completion of our performance obligation during year ended December 31, 2020, along with continued performance and delivery of services under the Janssen License and Collaboration Agreement.

We determined that the transaction price of the initial performance obligation under the Restated Agreement was $106.5 million as of December 31, 2021, an increase of $7.9 million from the transaction price of $98.6 million as of December 31, 2020, under the Original Agreement. In order to determine the transaction price, we evaluated all payments expected to be received during the duration of the contract, net of development costs reimbursement expected to be payable to Janssen. We determined that the transaction price included $87.5 million of nonrefundable payments received as of December 31, 2021, $17.9 million of reimbursement from Janssen for services performed for IL-23 receptor antagonist compound research and other services and estimated variable consideration consisting of $8.2 million of development cost reimbursement from Janssen, partially offset by $7.1 million of net cost reimbursement due to Janssen for services performed. The increase in transaction price from December 31, 2020 to December 31, 2021 was due primarily to reductions in both the remaining services to be performed by us under the Restated Agreement and the remaining shared development costs under the Restated Agreement.

Research and Development Expenses

	Year Ended December 31,		Dollar	%
	2021	2020	Change	Change
	(Dollars in thousands)			
Clinical and development expense—rusfertide (PTG-300)	$ 55,382	$ 32,395	$ 22,987	71
Clinical and development expense—PN-943	37,655	23,354	14,301	61
Clinical and development expense—JNJ-2113 (PN-235)	4,777	317	4,460	*
Clinical and development expense—PN-232	2,037	—	2,037	*
Clinical and development expense—PTG-200	23	925	(902)	(98)
Clinical and development expense—PTG-100	374	540	(166)	(31)
Pre-clinical and drug discovery research expense	24,943	18,453	6,490	35
Milestone payment obligation to former collaboration partner	4,000	—	4,000	*
Grants and tax incentives expense reimbursement, net	(3,185)	(1,478)	(1,707)	115
Total research and development expenses	$ 126,006	$ 74,506	$ 51,500	69

*Percentage not meaningful

Research and development expenses increased $51.5 million, or 69%, from $74.5 million for the year ended December 31, 2020 to $126.0 million for the year ended December 31, 2021. The increase was primarily due to an increase of $23.0 million in rusfertide clinical trial and development costs as clinical trials have enrolled and progressed, including the ongoing REVIVE and PACIFIC Phase 2 trials in PV, which began in December 2019 and the first quarter of 2021, respectively, and HH, which began in early 2020, and clinical and contract manufacturing activities incurred in 2021 in support of the REVIVE and PACIFIC Phase 2 trials and planned VERIFY global Phase 3 clinical trial of rusfertide in PV; an increase of $14.3 million in PN-943 clinical trial and development costs and contract manufacturing costs primarily related to the Phase 2 IDEAL trial in UC initiated during the second quarter of 2020; an increase of $6.5 million in preclinical and drug discovery research expenses; an increase of $4.5 million of clinical trial and development costs for the Phase 1 JNJ-2113 initiated in December 2020; an increase of $4.0 million of expenses related to milestone payments and obligations under the Zealand Agreement for rusfertide pursuant to the resolution of related arbitration; and an increase of $2.0 million of clinical trial and development costs for the Phase 1 PN-232 study initiated in May 2021. These increases were partially offset by a $1.7 million increase in grant and accrued refundable cash tax incentives and a decrease of $0.9 million in PTG-200 clinical trial and development expenses under the Janssen License

and Collaboration Agreement due to our delivery of substantially all agreed-upon services for the PTG-200 Phase 2 clinical trial prior to 2021.

We had 92 and 59 full-time equivalent research and development employees as of December 31, 2021 and 2020, respectively. Research and development expenses for the year ended December 31, 2021 included increases of $4.9 million in stock-based compensation expense and $5.3 million of other personnel-related expenses compared to the year ended December 31, 2020.

General and Administrative Expenses

General and administrative expenses increased $8.6 million, or 46%, from $18.6 million for the year ended December 31, 2020 to $27.2 million for the year ended December 31, 2021, primarily due to increases of $5.2 million in personnel-related expenses, $1.6 million in consulting expenses, $0.9 million in market research expenses, $0.5 million in recruiting expenses to support the growth of our business, and $0.3 million in insurance expense. The increase in personnel-related expenses was primarily due to an increase of $3.6 million in stock-based compensation expense and $1.6 million in wages and salaries.

We had 26 and 20 full-time equivalent general and administrative employees as of December 31, 2021 and 2020, respectively.

Interest Income

Interest income decreased $0.5 million, or 51%, from $0.9 million for the year ended December 31, 2020 to $0.4 million for the year ended December 31, 2021. This decrease was primarily due to the low interest rate environment in 2021 and a change in the mix of marketable securities compared to the prior year period, despite higher interest-earning asset balances.

Interest Expense

Interest expense of $0.6 million for the year ended December 31, 2020 was comprised of interest expense on our long-term debt under our term credit facility. We prepaid our outstanding long-term debt under our term credit facility during the second quarter of 2020. We executed a payoff letter to release all obligations under the term credit facility during the third quarter of 2021.

Loss on Early Repayment of Debt

Loss on early repayment of debt of $0.6 million for the year ended December 31, 2020 was comprised of prepayment and final payment fees paid in connection with the early repayment of our term loan in June 2020. We had no debt outstanding at December 31, 2021.

Other Expense, Net

Other expense, net was $0.1 million for the year ended December 31, 2021 compared to zero for the year ended December 31, 2020. The change was due primarily to an increase in foreign exchange losses.

Income Tax Expense

Income tax expense decreased $1.3 million, or 100%, from $1.3 million for the year ended December 31, 2020 to zero for the year ended December 31, 2021. Our effective income tax rate was 0% for the year ended December 31, 2021 as compared to 2.0% for the year ended December 31, 2020. Our effective income tax rate differed from our federal statutory rate of 21% primarily because our losses could not be benefited due to our full valuation allowance position. During the second quarter of 2020, our Australia subsidiary sold beneficial rights to discovery intellectual property to our U.S. entity, and the U.S. entity reimbursed the Australia subsidiary for certain direct development costs.

Upon completion of the sale, we analyzed tax planning strategies and future income and concluded that a valuation allowance was necessary for our Australia subsidiary. Income tax expense for the year ended December 31, 2020 reflected the sale of intellectual property rights, cost reimbursements and related adjustments to the deferred tax asset, establishment of a valuation allowance and certain uncertain tax position liabilities. We maintained a full valuation allowance on our tax position at December 31, 2021.

Liquidity and Capital Resources

Liquidity and Capital Expenditures

Sources of Liquidity

Historically, we have funded our operations primarily from net proceeds from the sale of shares of our common stock and receipt of payments under collaboration agreements.

In August 2022, we entered into an Open Market Sale Agreement℠ (the "Sales Agreement"), pursuant to which we may offer and sell up to $100.0 million of shares of our common stock from time to time in "at-the-market" offerings (the "2022 ATM Facility"). As of December 31, 2022, no sales were made under the 2022 ATM Facility.

In June 2021, we completed an underwritten public offering of 3,046,358 shares of common stock at a public offering price of $37.75 per share and issued an additional 456,953 shares of common stock at a public offering price of $37.75 per share following the underwriters' exercise of their option to purchase additional shares. Net proceeds, after deducting underwriting commission and offering costs paid by us, were $123.8 million.

In December 2020, we completed an underwritten public offering of 4,761,904 shares of common stock at a public offering price of $21.00 per share and issued an additional 714,285 shares of our common stock at a price of $21.00 per share following the underwriters' exercise of their option to purchase additional shares. Net proceeds, after deducting underwriting commissions and offering costs paid by us, were $107.6 million.

In May 2020, we completed an underwritten public offering of 7,000,000 shares of our common stock at a public offering price of $14.00 per share, and we issued an additional 1,050,000 shares of our common stock at a price of $14.00 per share following the underwriters' exercise of their option to purchase additional shares. Net proceeds, after deducting underwriting commissions and offering costs paid by us, were $105.3 million.

In November 2019, we entered into an Open Market Sale Agreement℠ (the "Prior Sales Agreement"), pursuant to which we could offer and sell up to $75.0 million of shares of our common stock from time to time in "at-the-market" offerings (the "2019 ATM Facility"). During the year ended December 31, 2020, we sold 2,483,719 shares under the 2019 ATM Facility for net proceeds of $41.9 million. No shares were sold under the 2019 ATM Facility during the year ended December 31, 2021. During the year ended December 31, 2022, we sold 422,367 shares of our common stock under the 2019 ATM Facility for net proceeds of $14.6 million. The Prior Sales Agreement was terminated in connection with and replaced by the Sales Agreement in August 2022.

We have received a total of $112.5 million in non-refundable payments from Janssen since the inception of the Janssen License and Collaboration Agreement in 2017 through December 31, 2022, as follows:

- Upon effectiveness of the Original Agreement, we received a non-refundable, upfront cash payment of $50.0 million from Janssen;

- Upon effectiveness of the First Amendment, we became eligible to receive a $25.0 million payment from Janssen, which was received during the second quarter of 2019;

- In December 2019, we became eligible to receive a $5.0 million payment triggered by the successful nomination of a second-generation development compound, which was received during the first quarter of 2020;

- In October 2021, we became eligible to receive $7.5 million milestone payment from Janssen triggered by completion of the data collection for JNJ-2113 (formerly known as PN-235) Phase 1 activities, which was received during the fourth quarter of 2021; and

- In March 2022, we became eligible to receive a $25.0 million milestone payment in connection with the dosing of the third patient in the Phase 2b clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis during the first quarter of 2022, which was received during the second quarter of 2022.

We also expect to receive payments for services provided under the collaboration agreement and we may make in-kind payment reimbursements to Janssen for certain costs they have incurred pursuant to the cost sharing terms of the agreement.

Pursuant to the Restated Agreement, we may be eligible to receive clinical development, regulatory and sales milestones, if and when achieved. Upcoming potential development milestones for second-generation products include:

- $10.0 million upon the dosing of the third patient in the first Phase 2 clinical trial for any second-generation product for a second indication (i.e., an indication different than the indication which triggered the $25.0 million milestone payment received during the first quarter of 2022 described above);

- $50.0 million upon the dosing of the third patient in a Phase 3 clinical trial for a second-generation compound for any indication;

- $15.0 million upon the dosing of the third patient in a Phase 3 clinical trial for a second-generation compound for a second indication; and

- $115.0 million upon a Phase 3 clinical trial for a second-generation compound for any indication meeting its primary clinical endpoint.

Capital Requirements

As of December 31, 2022, we had $237.4 million of cash, cash equivalents and marketable securities and an accumulated deficit of $536.8 million. Our capital expenditures were $0.8 million, $1.1 million and $0.5 million for the years ended December 31, 2022, 2021 and 2020, respectively. Our primary uses of cash are to fund our operating expenses, primarily related to our research and development expenditures, general and administrative costs and pre-commercialization costs. Cash used in operating activities is impacted by the timing of when we pay these expenses. As of the date of this filing, we believe, based on our current operating plan and assumptions that our existing cash, cash equivalents and marketable securities will be sufficient to meet our anticipated operating and capital expenditure requirements for at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong. We could utilize our available capital resources sooner than we currently expect if, for instance, our planned pre-clinical and clinical trials are successful or expanded, our product candidates enter new and more advanced stages of clinical development, we experience significant delays or difficulties in commencing, enrolling or completing clinical studies, our newer product clinical trials advance beyond the discovery stage, or various other factors. We expect that our cash burn will be lower in 2023 due to our research and development expenses decreasing in the near term as we continue to de-prioritize our PN-943 clinical program and streamline certain discovery programs to focus our resources toward progressing our rusfertide program into later stage clinical trials and preparing for commercialization.

We anticipate that we will need to raise substantial additional funding to advance rusfertide through clinical development and toward potential regulatory approval and to develop, acquire, or in-license other potential product candidates. Our future funding requirements will depend on many factors, including:

- the progress, timing, scope, results and costs of advancing our clinical trials for our product candidates, including the ability to enroll patients in a timely manner for our clinical trials;
- the costs of and our ability to obtain clinical and commercial supplies and any other product candidates we may identify and develop;
- our ability to successfully commercialize the product candidates we may identify and develop;
- the selling and marketing costs associated with our current product candidates and any other product candidates we may identify and develop, including the costs and timing of expanding our sales and marketing capabilities;
- the achievement of development, regulatory and sales milestones resulting in payments to us from Janssen under the Restated Agreement or other such arrangements that we may enter into, and the timing of such payments, if any;
- the timing, receipt and amount of royalties under the Restated Agreement on worldwide net sales of IL-23 receptor antagonist compounds, upon regulatory approval or clearance, if any;
- the amount and timing of sales and other revenues from our current product candidates and any other product candidates we may identify and develop, including the sales price and the availability of adequate third-party reimbursement;
- the cash requirements of any future acquisitions or discoveries of product candidates;
- the time and costs necessary to respond to technological and market developments;
- the extent to which we may acquire or in-license other product candidates and technologies;
- the costs necessary to attract, hire and retain qualified personnel;
- the costs of maintaining, expanding and protecting our intellectual property portfolio; and
- the costs of ongoing general and administrative activities to support the growth of our business.

Such additional funding may come from various sources, including raising additional capital, seeking access to debt, and seeking additional collaborative or other arrangements with partners, but such funding may not be available on terms acceptable to us, if at all. As discussed in Part I, Item1A."Risk Factors", we are currently operating in a period of economic uncertainty and capital markets disruption, which has been significantly impacted by domestic and global monetary and fiscal policy, and geopolitical instability, among other factors. A future recession or market correction related to COVID-19 or due to other factors, including significant geopolitical or macroeconomic events, could materially affect our business and our access to credit and financial markets.

Any failure to raise capital as and when needed could have a negative impact on our financial condition and on our ability to pursue our business plans and strategies. Further, our operating plans may change, and we may need additional funds to meet operational needs and capital requirements for clinical trials, other research and development activities and pre-commercialization costs. If we do raise additional capital through public or private equity offerings or convertible debt securities, the ownership interest of our existing stockholders could be diluted, and the terms of these securities

could include liquidation or other preferences that could adversely affect our stockholders' rights. If we raise additional capital through debt financing, we could be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to fully estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated product development programs. For additional information, see Part I, Item 1A, Risk Factors—"Risks Related to our Financial Position and Capital Requirements".

The following table includes our cash flow data for the periods indicated (in thousands):

Consolidated Statements of Cash Flows Data:	Year Ended December 31,		
	2022	2021	2020
	(Dollars in thousands)		
Cash used in operating activities	$ (108,137)	$ (107,865)	$ (72,484)
Cash provided by (used in) investing activities	$ 91,468	$ (15,860)	$ (90,965)
Cash provided by financing activities	$ 18,838	$ 129,923	$ 247,626
Stock-based compensation	$ 24,202	$ 16,395	$ 7,899

Cash Used in Operating Activities

Cash used in operating activities during the year ended December 31, 2022, was $108.1 million, consisting primarily of our net loss of $127.4 million and a net change of $7.8 million in net operating assets and liabilities, partially offset by certain non-cash items, including $24.2 million of stock-based compensation expense. The $0.3 million increase in cash flow used in operating activities during the year ended December 31, 2022, as compared to the year ended December 31, 2021, was primarily due to a $1.8 million increase in our net loss, a $4.5 million net change in net operating assets and liabilities, and a $1.8 million net change in other non-cash items, partially offset by a $7.8 million increase in stock-based compensation expense.

Cash used in operating activities during the year ended December 31, 2021, of $107.9 million consisted primarily of our net loss of $125.6 million, partially offset by certain non-cash items including $16.4 million of stock-based compensation expense. The $35.4 million increase in cash flow used in operating activities during the year ended December 31, 2021, as compared to the year ended December 31, 2020, was primarily due to a $59.4 million increase in our net loss, partially offset by certain non-cash items including an increase of $8.5 million of stock-based compensation expense, and a $14.2 million change in decrease in deferred revenue.

Cash Provided by (Used in) Investing Activities

Cash provided by investing activities for the year ended December 31, 2022, was $91.5 million, consisting of proceeds from maturities of marketable securities of $307.1 million, partially offset by purchases of marketable securities of $214.9 million and purchases of property and equipment of $0.8 million. The $107.3 million increase in cash provided by investing activities for the year ended December 31, 2022, as compared to the year ended December 31, 2021, was primarily related to a decrease of $71.7 million in purchases of marketable securities and an increase of $35.3 million in proceeds from maturities of marketable securities. Purchases of property and equipment were primarily related to purchases of laboratory and computer equipment.

Cash used in investing activities for the year ended December 31, 2021, was $15.9 million, consisting of purchases of marketable securities of $286.6 million and purchases of property and equipment of $1.1 million, partially offset by proceeds from maturities of marketable securities of $271.8 million. The $75.1 million decrease in cash used in investing activities for the year ended December 31, 2021, as compared to the year ended December 31, 2020, was primarily due to an increase of $82.3 million in proceeds from maturities of marketable securities. Purchases of property and equipment were primarily related to purchases of laboratory equipment, furniture and computer equipment.

Cash Provided by Financing Activities

Cash provided by financing activities for the year ended December 31, 2022, was $18.8 million, consisting primarily of net cash proceeds from sales of $14.6 million under the 2019 ATM Facility and proceeds from the issuance of common stock upon the exercise of stock options and purchases of common stock under our employee stock purchase plan of $4.4 million. The $111.1 million decrease in cash provided by financing activities for the year ended December 31, 2022, as compared to the year ended December 31, 2021, was primarily due to a $123.8 million decrease in cash proceeds from our public offerings of common stock, and a $1.8 million decrease in proceeds from the issuance of common stock upon exercise of stock options and purchases of common stock under our employee stock purchase plan. These decreases were partially offset by $14.6 million increase in cash proceeds from ATM sales.

Cash provided by financing activities for the year ended December 31, 2021, was $129.9 million, consisting primarily of cash proceeds from our public offerings of common stock of $123.8 million and proceeds from the issuance of common stock upon the exercise of stock options and purchases of common stock under our employee stock purchase plan of $6.3 million. The $117.7 million decrease in cash provided by financing activities for the year ended December 31, 2021, as compared to the year ended December 31, 2020, was primarily due to an $89.5 million decrease in cash proceeds from our public offerings of common stock, a $42.1 million decrease in cash proceeds from ATM sales. These decreases were partially offset by $10.5 million related to the early repayment of long-term debt in 2020 and a $3.5 million increase in proceeds from the issuance of common stock upon exercise of stock options and purchases of common stock under our employee stock purchase plan.

Contractual Obligations and Other Commitments

In the normal course of business, we enter into agreements with contract service providers to assist in the performance of our research and development activities and clinical and commercial manufacturing activities. Subject to required notice periods and our obligations under binding commitments, we can elect to discontinue the work under these agreements at any time. We expect to enter into additional clinical development, contract research, clinical and commercial manufacturing, supplier agreements and collaborative research agreements in the future, which may require upfront payments and long-term commitments of capital resources.

Our contractual obligations include minimum lease payments under our operating lease obligations. On July 2, 2021, we entered into a second amendment to our facility lease agreement dated as of March 2017, to lease approximately 15,000 square feet of additional office space in Newark, California. See Note 10 to the Consolidated Financial Statements elsewhere in this Annual Report on Form 10-K for additional information.

Under the Restated Agreement, we share with Janssen certain development, regulatory and compound supply costs. The actual amounts that we pay Janssen or that Janssen pays us will depend on numerous factors, some of which are outside of our control and some of which are contingent upon the success, if achieved, of certain development and regulatory activities. See Note 3 to the Consolidated Financial Statements elsewhere in this Annual Report on Form 10-K for additional information.

In June 2012, we entered into the Zealand Agreement to identify, optimize and develop novel disulfide-rich peptides to discover a hepcidin mimetic. We amended the Zealand Agreement on February 28, 2014, at which point we assumed responsibility for the development program. On January 23, 2020, we initiated arbitration proceedings with the International Court of Arbitration of the International Chamber of Commerce against Zealand. On August 4, 2021, we and Zealand agreed to resolve the dispute and reached an Arbitration Resolution Agreement. See Note 7 and Note 11 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risks in the ordinary course of our business. These risks primarily include interest rate sensitivities related to our interest-earning investments and inflation risk affecting labor costs and clinical trial costs.

Interest Rate Fluctuation Risk

We had $237.4 million and $326.9 million in cash, cash equivalents and marketable securities at December 31, 2022 and 2021, respectively. Our cash and cash equivalents consist of cash, money market funds, commercial paper and government bonds. Marketable securities consist of corporate bonds, commercial paper, government bonds and highly rated supranational and sovereign government securities. A portion of our investments may be subject to interest rate risk and could fall in value if market interest rates continue to increase. Based on our interest rate sensitivity analysis, a hypothetical 100 basis point increase in interest rates would increase our interest income by approximately $1.8 million, while an immediate 100 basis point decrease in interest rates would decrease our interest income by approximately $2.3 million.

Approximately $2.5 million and $1.1 million of our cash balance was located in Australia at December 31, 2022 and 2021, respectively. Our expenses, except those related to our Australian operations, are generally denominated in U.S. dollars. For our operations in Australia, the majority of our expenses are denominated in Australian dollars. To date, we have not had a formal hedging program with respect to foreign currency, but we may do so in the future if our exposure to foreign currency becomes more significant. A 10% increase or decrease in current exchange rates would not have a material effect on our results of operations.

Inflation Fluctuation Risk

Inflation has increased during the period covered by this report and is expected to continue to at elevated levels or even increase for the near future. Inflation generally affects us by increasing our costs, such as the cost of labor and research and development contract costs. We do not believe inflation has had a material effect on our results of operations during the year ended December 31, 2022.

Item 8. Financial Statements and Supplementary Data

PROTAGONIST THERAPEUTICS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Protagonist Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Protagonist Therapeutics, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements 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 audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the 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 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 financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relate to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of critical audit matter 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 separate opinions on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued clinical and research related expenses

Description of the Matter

At December 31, 2022, the Company has accrued $19.1 million of clinical and research related expenses. As described in Note 2 to the consolidated financial statements, the Company records estimated costs of research and development activities conducted by third-party service providers, which include the conduct of pre-clinical studies and clinical trials, and contract manufacturing activities, based upon the estimated amount of services provided but not yet invoiced. The Company accrues for these costs based on factors such as estimates of the work completed and in accordance with agreements established with its third-party service providers.

Auditing management's accounting for accrued clinical development cost is especially challenging because the evaluation is dependent on a high volume of data exchanged between third-party service providers, internal clinical personnel, and the Company's finance department. The accrued amounts are determined based on an evaluation of the unique terms and conditions set forth in each respective agreement. Additionally, due to the duration of clinical trial activities and the timing of invoices received from third parties, the calculation of the accrual for services incurred requires management to determine that they have complete and accurate information from its vendors.

How We Addressed the Matter in Our Audit

To test accrued clinical development costs, our audit procedures included, among others, testing the accuracy and completeness of the inputs used in management's analysis to determine costs incurred. We also inspected terms and conditions for selected research and development contracts and change orders and compared these to the cost models management used in tracking progress of service agreements. We met with the Company's internal clinical personnel to understand the status of significant clinical activities. We evaluated services incurred by third parties by understanding the terms and timeline of significant projects, and evaluating management's determination of work performed, subjects enrolled, sites activated and costs incurred. Further, we inspected selected invoices received from third parties after the balance sheet date and evaluated whether services performed prior to the balance sheet date had been properly included in costs accrued.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2020.
San Mateo, California
March 15, 2023

PROTAGONIST THERAPEUTICS, INC.
Consolidated Balance Sheets
(In thousands, except share data)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 125,744	$ 123,665
Marketable securities	111,611	203,235
Receivable from collaboration partner—related party	10	1,566
Research and development tax incentive receivable	—	2,792
Prepaid expenses and other current assets	5,712	9,478
Total current assets	243,077	340,736
Property and equipment, net	1,565	1,798
Restricted cash—noncurrent	225	225
Operating lease right-of-use asset	3,061	4,936
Total assets	$ 247,928	$ 347,695
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 3,640	$ 1,600
Payable to collaboration partner—related party	69	899
Accrued expenses and other payables	24,955	37,716
Deferred revenue—related party	—	1,601
Operating lease liability—current	2,515	2,200
Total current liabilities	31,179	44,016
Operating lease liability—noncurrent	1,141	3,658
Total liabilities	32,320	47,674
Commitments and contingencies		
Stockholders' equity:		
Preferred stock, $0.00001 par value, 10,000,000 shares authorized; no shares issued and outstanding	—	—
Common stock, $0.00001 par value, 90,000,000 shares authorized; 49,339,252 and 47,838,330 shares issued and outstanding as of December 31, 2022 and 2021, respectively	—	—
Additional paid-in capital	752,722	709,682
Accumulated other comprehensive loss	(359)	(299)
Accumulated deficit	(536,755)	(409,362)
Total stockholders' equity	215,608	300,021
Total liabilities and stockholders' equity	$ 247,928	$ 347,695

The accompanying notes are an integral part of these consolidated financial statements.

PROTAGONIST THERAPEUTICS, INC.
Consolidated Statements of Operations
(In thousands, except share and per share data)

	Year Ended December 31,		
	2022	2021	2020
License and collaboration revenue—related party	$ 26,581	$ 27,357	$ 28,628
Operating expenses:			
Research and development	126,215	126,006	74,506
General and administrative	31,739	27,196	18,638
Total operating expenses	157,954	153,202	93,144
Loss from operations	(131,373)	(125,845)	(64,516)
Interest income	4,060	443	900
Interest expense	—	—	(598)
Loss on early repayment of debt	—	—	(585)
Other expense, net	(80)	(149)	(46)
Loss before income tax expense	(127,393)	(125,551)	(64,845)
Income tax expense	—	—	(1,305)
Net loss	$ (127,393)	$ (125,551)	$ (66,150)
Net loss per share, basic and diluted	$ (2.60)	$ (2.71)	$ (1.92)
Weighted-average shares used to compute net loss per share, basic and diluted	49,042,232	46,322,910	34,396,446

The accompanying notes are an integral part of these consolidated financial statements.

PROTAGONIST THERAPEUTICS, INC.
Consolidated Statements of Comprehensive Loss
(In thousands)

	Year Ended December 31,		
	2022	2021	2020
Net loss	$ (127,393)	$ (125,551)	$ (66,150)
Other comprehensive loss:			
Loss (gain) on translation of foreign operations	(149)	(182)	266
Unrealized gain (loss) on marketable securities	89	(145)	(17)
Comprehensive loss	$ (127,453)	$ (125,878)	$ (65,901)

The accompanying notes are an integral part of these consolidated financial statements.

PROTAGONIST THERAPEUTICS, INC.
Consolidated Statements of Stockholders' Equity
(In thousands, except share data)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Gain	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2019	27,217,649	$ —	$ 297,846	$ (221)	$ (217,661)	$ 79,964
Issuance of common stock pursuant to public offerings, net of issuance costs	13,526,189	—	212,974	—	—	212,974
Issuance of common stock pursuant to at-the-market offering, net of issuance costs	2,483,719	—	41,871	—	—	41,871
Issuance of common stock under equity incentive and employee stock purchase plans	517,908	—	2,799	—	—	2,799
Stock-based compensation expense	—	—	7,899	—	—	7,899
Other comprehensive gain	—	—	—	249	—	249
Net loss	—	—	—	—	(66,150)	(66,150)
Balance at December 31, 2020	43,745,465	—	563,389	28	(283,811)	279,606
Issuance of common stock pursuant to public offerings, net of issuance costs	3,503,311	—	123,804	—	—	123,804
Issuance of common stock under equity incentive and employee stock purchase plans	596,614	—	6,283	—	—	6,283
Shares withheld for net settlement of tax withholding upon vesting of restricted stock units	(7,060)	—	(189)	—	—	(189)
Stock-based compensation expense	—	—	16,395	—	—	16,395
Other comprehensive loss	—	—	—	(327)	—	(327)
Net loss	—	—	—	—	(125,551)	(125,551)
Balance at December 31, 2021	47,838,330	—	709,682	(299)	(409,362)	300,021
Issuance of common stock pursuant to at-the-market offering, net of issuance costs	422,367	—	14,553	—	—	14,553
Issuance of common stock under equity incentive and employee stock purchase plans	686,284	—	4,448	—	—	4,448
Issuance of common stock upon exercise of Exchange Warrants	399,997	—	—	—	—	—
Shares withheld for net settlement of tax withholding upon vesting of restricted stock units	(7,726)	—	(188)	—	—	(188)
Stock-based compensation expense	—	—	24,202	—	—	24,202
Issuance costs related to prior period common stock offering	—	—	25	—	—	25
Other comprehensive loss	—	—	—	(60)	—	(60)
Net loss	—	—	—	—	(127,393)	(127,393)
Balance at December 31, 2022	49,339,252	$ —	$ 752,722	$ (359)	$ (536,755)	$ 215,608

The accompanying notes are an integral part of these consolidated financial statements.

PROTAGONIST THERAPEUTICS, INC.
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,		
	2022	**2021**	**2020**
Cash Flows from Operating Activities			
Net loss	$ (127,393)	$ (125,551)	$ (66,150)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation	24,202	16,395	7,899
Operating lease right-of-use asset amortization	2,335	1,962	1,775
Net amortization of (discount) premium on marketable securities	(549)	1,830	37
Depreciation and amortization	1,034	813	948
Change in deferred tax asset	—	—	1,438
Loss on early repayment of debt	—	—	585
Changes in operating assets and liabilities:			
Research and development tax incentive receivable	2,686	(1,775)	(990)
Receivable from collaboration partner—related party	1,556	860	4,329
Prepaid expenses and other assets	3,754	(3,227)	(1,102)
Accounts payable	2,045	(1,390)	309
Payable to collaboration partner—related party	(830)	(1,833)	1,471
Accrued expenses and other payables	(12,715)	19,097	5,840
Deferred revenue—related party	(1,601)	(12,876)	(27,053)
Operating lease liability	(2,661)	(2,049)	(1,941)
Other liabilities	—	(121)	121
Net cash used in operating activities	(108,137)	(107,865)	(72,484)
Cash Flows from Investing Activities			
Purchase of marketable securities	(214,874)	(286,589)	(280,027)
Proceeds from maturities of marketable securities	307,137	271,830	189,533
Purchases of property and equipment	(795)	(1,101)	(471)
Net cash provided by (used in) investing activities	91,468	(15,860)	(90,965)
Cash Flows from Financing Activities			
Proceeds from public offering of common stock, net of issuance costs	—	123,829	213,303
Proceeds from at-the-market offering, net of issuance costs	14,553	—	42,062
Proceeds from issuance of common stock upon exercise of stock options and purchases under employee stock purchase plan	4,448	6,283	2,799
Tax withholding payments related to net settlement of restricted stock units	(188)	(189)	—
Issuance costs related to prior period common stock offering	25	—	—
Early repayment of long-term debt	—	—	(10,524)
Issuance costs related to long-term debt	—	—	(14)
Net cash provided by financing activities	18,838	129,923	247,626
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(90)	(126)	175
Net increase in cash, cash equivalents and restricted cash	2,079	6,072	84,352
Cash, cash equivalents and restricted cash, beginning of period	123,890	117,818	33,466
Cash, cash equivalents and restricted cash, end of period	$ 125,969	$ 123,890	$ 117,818
Supplemental Disclosure of Cash Flow Information:			
Cash paid for interest	$ —	$ —	$ 438
Supplemental Disclosure of Non-Cash Financing and Investing Information:			
Purchases of property and equipment in accounts payable and accrued liabilities	$ 19	$ 143	$ 85
Issuance costs related to common stock offering included in accrued liabilities and other payables	$ —	$ 25	$ 205
Issuance costs related to at-the-market offering of common stock included in prepaid expenses and other assets at the end of the previous year	$ —	$ —	$ 191
Issuance costs related to common stock offering included in prepaid expenses and other assets at the end of the previous year	$ —	$ —	$ 124

The accompanying notes are an integral part of these consolidated financial statements.

Note 1. Organization and Description of Business

Protagonist Therapeutics, Inc. (the "Company") is headquartered in Newark, California. The Company is a biopharmaceutical company with peptide-based new chemical entities rusfertide and JNJ-2113 (formerly known as PN-235) in different stages of clinical development, all derived from the Company's proprietary technology platform. The Company's clinical programs fall into two broad categories of diseases: (i) hematology and blood disorders, and (ii) inflammatory and immunomodulatory diseases. Protagonist Pty Limited ("Protagonist Australia") is a wholly-owned subsidiary of the Company and is located in Brisbane, Queensland, Australia.

Operating segments are components of an enterprise for which separate financial information is available and is evaluated regularly by the Chief Executive Officer, the Company's chief operating decision maker, in deciding how to allocate resources and assessing performance. The Company operates and manages its business as one operating segment. The Company's Chief Executive Officer reviews financial information on an aggregate basis for the purposes of allocating and evaluating financial performance.

Substantially all of the Company's long-lived assets are maintained in the United States.

Liquidity

As of December 31, 2022, the Company had cash, cash equivalents and marketable securities of $237.4 million. The Company has incurred net losses from operations since inception and had an accumulated deficit of $536.8 million as of December 31, 2022. The Company's ultimate success depends upon the outcome of its research and development and collaboration activities. The Company expects to incur additional losses in the future and anticipates the need to raise additional capital to continue to execute its long-range business plan. Since the Company's initial public offering in August 2016, it has financed its operations primarily through proceeds from offerings of common stock and payments received under license and collaboration agreements.

Risks and Uncertainties

The Company is subject to risks and uncertainties as a result of the prolonged nature of the COVID-19 pandemic and emergent variants with increased transmissibility, even in those who are fully vaccinated. The future impact on the Company's activities will depend on a number of factors, including, but not limited to, the scope and magnitude of any resurgences in the outbreak and the spread of COVID-19 variants, the timing, extent, effectiveness and durability of COVID-19 vaccine programs or other treatments; and new travel and other restrictions and public health measures. The Company has experienced delays in its existing and planned clinical trials due to worldwide impacts related to the pandemic. The Company's future results of operations and liquidity could be adversely impacted by further delays in existing and planned clinical trials, continued difficulty in recruiting patients for these clinical trials, delays in manufacturing and collaboration activities, supply chain disruptions, and the ongoing impact on its operating activities and employees. In addition, a recession or market correction related to or amplified by COVID-19 could materially affect the Company's business.

The Company is currently operating in a period of economic uncertainty and capital markets disruption, which has been impacted by domestic and global monetary and fiscal policy, geopolitical instability, including an ongoing military conflict between Russia and Ukraine and the rising tensions between China and Taiwan, a recessionary environment and historically high domestic and global inflation. In particular, the conflict in Ukraine has exacerbated market disruptions, including significant volatility in commodity prices, as well as supply chain interruptions, and has contributed to record inflation globally. The U.S. Federal Reserve and other central banks may be unable to contain inflation through more restrictive monetary policy, and inflation may increase or continue for a prolonged period of time. Inflationary factors, such as increases in the cost of clinical supplies, interest rates, overhead costs and transportation costs may adversely affect the Company's operating results. The Company continues to monitor these events and the potential impact on its business. Although the Company does not believe that inflation has had a material impact on its financial position or

results of operations to date, it may be adversely affected in the future due to domestic and global monetary and fiscal policy, supply chain constraints, consequences associated with COVID-19 and the ongoing conflict between Russia and Ukraine and other factors, and such factors may lead to increases in the cost of manufacturing for and initiation of studies in the Company's product candidates.

Note 2. Summary of Significant Accounting Policies

Basis of Presentation and Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly owned subsidiary, Protagonist Australia, and have been prepared in conformity with accounting principles generally accepted in the United States ("GAAP"). All intercompany balances and transactions have been eliminated upon consolidation.

The financial statements of Protagonist Australia use the Australian dollar as the functional currency since the majority of expense transactions occur in such currency. Gains and losses from foreign currency transactions were not material for all periods presented. The re-measurement from Australian dollar to U.S. dollars is outlined below:

a. Equity accounts, except for the change in retained earnings during the year, have been translated using historical exchange rates.

b. All other Australian dollar denominated assets and liabilities as of December 31, 2022 and 2021 have been translated using the year-end exchange rate.

c. The consolidated statements of operations have been translated at the weighted average exchange rates in effect during each year.

Foreign currency translation gains and losses are reported as a component of stockholders' equity in accumulated other comprehensive loss on the consolidated balance sheets.

Use of Estimates

The preparation of the consolidated financial statements in conformity with GAAP requires management to make estimates, assumptions and judgments that affect the reported amounts of assets and liabilities and disclosure of contingent liabilities as of the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. On an ongoing basis, management evaluates its estimates, including those related to revenue recognition, accruals for research and development activities, stock-based compensation, income taxes, marketable securities and leases. Estimates related to revenue recognition include actual costs incurred versus total estimated costs of the Company's deliverables to determine percentage of completion in addition to the application and estimates of potential revenue constraints in the determination of the transaction price under its license and collaboration agreements. Management bases these estimates on historical and anticipated results, trends and various other assumptions that the Company believes are reasonable under the circumstances, including assumptions as to forecasted amounts and future events.

Due to the prolonged nature of the COVID-19 pandemic, military conflict between Ukraine and Russia, rising tensions between China and Taiwan and inflationary pressures, there has been uncertainty and disruption in the global economy and financial markets. The Company has taken into consideration any known impacts in its accounting estimates to date and is not aware of any additional specific events or circumstances that would require any additional updates to its estimates or judgments or a revision of the carrying value of its assets or liabilities as of the filing date of this Annual Report on Form 10-K. These estimates may change as new events occur and additional information is obtained.

Actual results could differ materially from these estimates under different assumptions or conditions.

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents and marketable securities. Substantially all of the Company's cash is held by two financial institutions that management believes are of high credit quality. Such deposits may, at times, exceed federally insured limits. The primary focus of the Company's investment strategy is to preserve capital and to meet liquidity requirements. The Company's cash equivalents and marketable securities are managed by external managers within the guidelines of the Company's investment policy. The Company's investment policy addresses the level of credit exposure by limiting concentration in any one corporate issuer and establishing a minimum allowable credit rating. To manage its credit risk exposure, the Company maintains its U.S. portfolio of cash equivalents and marketable securities in fixed income securities denominated and payable in U.S. dollars. Permissible investments of fixed income securities include obligations of the U.S. government and its agencies, money market instruments including commercial paper and negotiable certificates of deposit, and highly rated corporate debt obligations and money market funds, and highly rated supranational and sovereign government securities.

Cash Equivalents

Cash equivalents that are readily convertible to cash are stated at cost, which approximates fair value. The Company considers all highly liquid investments purchased with an original maturity of three months or less to be cash equivalents.

Restricted Cash

Restricted cash consists primarily of cash balances held as security in connection with a letter of credit related to the Company's facility lease entered into in March 2017, as subsequently amended. The letter of credit balance decreased from $0.5 million at December 31, 2020 to $0.2 million at December 31, 2021 and 2022 pursuant to the terms of the facility lease.

Cash as Reported in Consolidated Statements of Cash Flows

Cash as reported in the consolidated statements of cash flows includes the aggregate amounts of cash and cash equivalents and the restricted cash as presented on the consolidated balance sheets.

Cash as reported in the consolidated statements of cash flows consisted of (in thousands):

	December 31,		
	2022	2021	2020
Cash and cash equivalents	$ 125,744	$ 123,665	$ 117,358
Restricted cash—current	—	—	10
Restricted cash—noncurrent	225	225	450
Total cash reported on consolidated statements of cash flows	$ 125,969	$ 123,890	$ 117,818

Marketable Securities

All marketable securities have been classified as "available-for-sale" and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its marketable securities at the time of purchase and reevaluates such designation as of each balance sheet date. Short-term marketable securities have maturities greater than three months but not longer than 365 days as of the balance sheet date. Long-term marketable securities have maturities of 365 days or longer as of the balance sheet date. Unrealized gains and losses are excluded from earnings and are reported as a component of comprehensive loss. Realized gains and losses and declines in fair value judged to be other than temporary, if any, on available-for-sale securities are included in interest income. The cost of securities sold is based on the specific-identification method. Interest on marketable securities is included in interest income.

Fair Value of Financial Instruments

Fair value accounting is applied to all financial assets and liabilities that are recognized or disclosed at fair value in the consolidated financial statements on a recurring basis (at least annually). The carrying amount of the Company's financial instruments, including cash equivalents, receivables from its collaboration partner, accounts payable, payables to its collaboration partner and accrued expenses and other payables approximate fair value due to their short-term maturities. See Note 4. to the Consolidated Financial Statements for additional information regarding the fair value of the Company's other financial assets and liabilities.

Property and Equipment

Property and equipment are stated at cost, net of accumulated depreciation. Depreciation is computed using the straight-line method over the estimated useful lives of the assets, ranging from three to five years. Leasehold improvements are amortized over the shorter of the lease term or the estimated useful lives of the assets. Maintenance and repairs are charged to expense as incurred. When assets are retired or otherwise disposed of, the cost and accumulated depreciation are removed from the consolidated balance sheet and any resulting gain or loss is reflected in operations in the period realized.

Leases

The Company determines if an arrangement is a lease at inception. Pursuant to Accounting Standards Codification Topic 842, *Leases,* ("ASC 842"), operating leases are included in operating lease right-of-use ("ROU") assets, operating lease liabilities, and noncurrent operating lease liabilities on the consolidated balance sheets. Operating lease ROU assets and operating lease liabilities are recognized based on the present value of the future minimum lease payments over the lease term at commencement date. If the Company's leases do not provide an implicit rate, the Company uses its incremental borrowing rate based on the information available at commencement date in determining the present value of future payments. The operating lease ROU asset also includes any lease payments made and excludes lease incentives and initial direct costs incurred. Lease terms include options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. Lease expense for minimum lease payments is recognized on a straight-line basis over the lease term.

The Company records tenant improvement allowances as a reduction to the ROU asset with the impact of the decrease recognized prospectively over the remaining lease term. The leasehold improvements are amortized over the shorter of their useful life or the remaining term of the lease.

Impairment of Long-Lived Assets

The Company reviews long-lived assets, primarily comprised of property, equipment and operating lease ROU assets, for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability is measured by comparison of the carrying amount to the future net cash flows which the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured as the amount by which the carrying amount of the assets exceeds the projected discounted future net cash flows arising from the asset. There have been no such impairments of long-lived assets for any of the periods presented.

Comprehensive Loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity that result from transactions and economic events other than those from stockholders. The Company's foreign currency translation and unrealized gains and losses on available-for-sale securities represent the only components of other comprehensive loss that are excluded from reported net loss and that are presented in the consolidated statements of comprehensive loss.

Income Taxes

The Company uses the asset and liability method to account for income taxes in accordance with the authoritative guidance for income taxes. Under this method, deferred tax assets and liabilities are determined based on future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases, and tax loss and credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates applied to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in the period that includes the enactment date. A valuation allowance is established when necessary to reduce deferred tax assets to the amount expected to be realized.

The Company recognizes the effect of income tax positions only if those positions are more likely than not of being sustained. Recognized income tax positions are measured at the largest amount that is greater than a 50% likelihood of being realized. Changes in recognition or measurement are reflected in the period in which the change in judgment occurs. The Company records interest and penalties related to unrecognized tax benefits in income tax expense. To date, there have been no interest or penalties recorded in relation to unrecognized tax benefits.

Revenue Recognition

Under Accounting Standards Codification Topic 606, *Revenue from Contracts with Customers* ("ASC 606"), the Company recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the Company expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, the Company performs 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) the Company satisfies a performance obligation. The Company applies the five-step model to contracts when it is probable that the Company will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. At contract inception, the Company assesses the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligations when (or as) the performance obligations are satisfied. The Company constrains its estimate of the transaction price up to the amount (the "variable consideration constraint") that a significant reversal of recognized revenue is not probable.

Licenses of intellectual property: If a license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in an arrangement, the Company recognizes revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the customer and the customer is able to use and benefit from the license. For licenses that are bundled with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring proportional performance for purposes of recognizing revenue from non-refundable, upfront fees. The Company evaluates the measure of proportional performance each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement or amendment that includes development, regulatory or commercial milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price. ASC 606 suggests two alternatives to use when estimating the amount of variable consideration: the expected value method and the most likely amount method. Under the expected value method, an entity considers the sum of probability-weighted amounts in a range of possible consideration amounts. Under the most likely amount method, an entity considers the single most likely amount in a range of possible consideration amounts. Whichever method used should be consistently applied throughout the life of the contract; however, it is not necessary for the Company to use the same approach for all contracts. The Company expects to use the most likely amount method for development and regulatory milestone payments. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone

payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. If there is more than one performance obligation, the transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis. The Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each subsequent reporting period, the Company re-evaluates the probability or achievement of each such milestone and any related constraint, and if necessary, adjusts its estimates of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Any potential milestone payments that the Company determines are not associated with performance obligations as defined under the contract are excluded from the transaction price and are recognized as the triggering event occurs.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on the level of sales, where the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied).

Upfront payments and fees are recorded as deferred revenue upon receipt or when due and may require deferral of revenue recognition to a future period until the Company performs its obligations under these arrangements. Amounts payable to the Company are recorded as accounts receivable when the Company's right to consideration is unconditional. Amounts payable to the Company and not yet billed to the collaboration partner are recorded as contract assets. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is such that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less.

Contractual cost sharing payments made to a customer or collaboration partner are accounted for as a reduction to the transaction price if such payments are not related to distinct goods or services received from the customer or collaboration partner.

Contracts may be amended to account for changes in contract specifications and requirements. Contract modifications exist when the amendment either creates new, or changes existing, enforceable rights and obligations. When contract modifications create new performance obligations and the increase in consideration approximates the standalone selling price for goods and services related to such new performance obligations, as adjusted for specific facts and circumstances of the contract, the modification is considered to be a separate contract. If a contract modification is not accounted for as a separate contract, the Company accounts for the promised goods or services not yet transferred at the date of the contract modification (the remaining promised goods or services) prospectively, as if it were a termination of the existing contract and the creation of a new contract, if the remaining goods or services are distinct from the goods or services transferred on or before the date of the contract modification. The Company accounts for a contract modification as if it were a part of the existing contract if the remaining goods or services are not distinct and, therefore, form part of a single performance obligation that is partially satisfied at the date of the contract modification. In such case the effect that the contract modification has on the transaction price, and on the entity's measure of progress toward complete satisfaction of the performance obligation, is recognized as an adjustment to revenue (either as an increase in or a reduction of revenue) at the date of the contract modification (the adjustment to revenue is made on a cumulative catch-up basis).

Research and Development Costs

Research and development costs ("R&D") are expensed as incurred, unless there is an alternate future use in other research and development projects or otherwise. Research and development costs include salaries and benefits, stock-based compensation expense, laboratory supplies and facility-related overhead, outside contracted services, including clinical trial costs, manufacturing and process development costs for both clinical and pre-clinical materials, research costs, development milestone payments under license and collaboration agreements, and other consulting services.

The Company accrues for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of pre-clinical studies and clinical trials and contract manufacturing activities. The

Company records the estimated costs of research and development activities based upon the estimated services provided but not yet invoiced and includes these costs in accrued expenses and other payables in the consolidated balance sheets and within research and development expense in the consolidated statements of operations. The Company accrues for these costs based on various factors such as estimates of the work completed and in accordance with agreements established with its third-party service providers. As actual costs become known, the Company adjusts its accrued liabilities. The Company has not experienced any material differences between accrued liabilities and actual costs incurred. However, the status and timing of actual services performed, the number of patients enrolled, the rate of patient enrollment and the number and location of sites activated may vary from the Company's estimate and may result in adjustments to research and development expenses in future periods. Changes in these estimates that result in material changes to the Company's accruals could materially affect the Company's results of operations.

Research and Development Tax Incentive

The Company is eligible under the AusIndustry research and development tax incentive program to obtain either a refundable cash tax incentive or a taxable credit in the form of a non-cash tax incentive from the Australian Taxation Office ("ATO"). The refundable cash tax incentive is available to the Company on the basis of specific criteria with which the Company must comply. Specifically, the Company must have annual turnover of less than AUD 20.0 million and cannot be controlled by income tax exempt entities. The refundable cash tax incentive is recognized as a reduction to research and development expense when the right to receive has been attained and funds are considered to be collectible. The Company may alternatively be eligible for a taxable credit in the form of a non-cash tax incentive in years when the annual turnover exceeds the limit. The Company evaluates its eligibility under tax incentive programs as of each balance sheet date and makes accrual and related adjustments based on the most current and relevant data available.

Stock-based Compensation

The Company measures its stock-based awards made to its equity plan participants based on the estimated fair values of the awards as of the grant date. For stock option awards, the Company uses the Black-Scholes option-pricing model to estimate fair values. For restricted stock unit awards, the estimated fair value is generally the fair market value of the underlying stock on the grant date. Stock-based compensation expense is recognized over the requisite service period and is based on the value of the portion of stock-based payment awards that is ultimately expected to vest. The Company recognizes forfeitures of stock-based awards as they occur.

The Company has granted performance share units ("PSUs") to certain executives of the Company. Stock-based compensation expense associated with PSUs is based on the fair value of the Company's common stock on the grant date, which equals the closing price of the Company's common stock on the grant date. The Company recognizes compensation expense over the vesting periods of the awards that are ultimately expected to vest when the achievement of the related performance obligation becomes probable.

If stock-based awards are granted in contemplation of or shortly before a planned release of material nonpublic information, and such information is expected to result in a material increase in the Company's share price, the Company considers whether an adjustment to the observable market price is required when estimating fair values.

Net Loss per Share

Basic net loss per share is calculated by dividing the Company's net loss by the weighted average number of shares of common stock and Exchange Warrants (as defined in Note 12. Stockholders' Equity below) outstanding during the period, without consideration of potentially dilutive securities. In accordance with Accounting Standards Codification Topic 260, *Earnings Per Share*, outstanding Exchange Warrants are included in the computation of basic net loss per share because the exercise price is negligible, and they are fully vested and exercisable after the original issuance date. Diluted net loss per share is the same as basic net loss per share for all periods presented since the effect of potentially dilutive securities is anti-dilutive given the net loss of the Company in each period. See Note 12. Stockholders' Equity for additional information regarding the Exchange Warrants.

Recently Issued Accounting Pronouncements Not Yet Adopted as of December 31, 2022

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments—Credit Losses (Topic 326)*, which is intended to provide more useful information about expected credit losses on financial assets held by a reporting entity at each reporting date. The new standard replaces the existing incurred loss impairment methodology with a methodology that requires consideration of a broader range of reasonable and supportable forward-looking information to estimate all expected credit losses. This guidance was originally effective for fiscal years and interim periods beginning after December 15, 2019, with early adoption permitted for fiscal years and interim periods beginning after December 15, 2018. In November 2019, the FASB issued ASU No. 2019-10, *Financial Instruments—Credit Losses (Topic 326), Derivatives and Hedging (Topic 815), and Leases (Topic 842): Effective Dates*, which amended the mandatory effective date of ASU No. 2016-13 for smaller reporting companies. Based on the Company's status as a smaller reporting company as of November 15, 2019, ASU 2016-13 is effective for the Company for fiscal years and interim periods beginning after December 15, 2022. The Company does not expect the adoption of this new guidance to have a material impact on its consolidated financial statements and related disclosures.

Note 3. License and Collaboration Agreement

Agreement Terms

On July 27, 2021, the Company entered into an Amended and Restated License and Collaboration Agreement (the "Restated Agreement") with Janssen Biotech, Inc., a Pennsylvania corporation ("Janssen") which amended and restated the License and Collaboration Agreement, effective July 13, 2017, by and between the Company (the "Original Agreement"), as amended by the first amendment, effective May 7, 2019 (the "First Amendment"). Janssen is a related party to the Company as Johnson & Johnson Innovation—JJDC, Inc., a significant stockholder of the Company, and Janssen are both subsidiaries of Johnson & Johnson. Upon the effectiveness of the Original Agreement, the Company received a non-refundable, upfront cash payment of $50.0 million from Janssen. Upon the effectiveness of the First Amendment, the Company received a $25.0 million payment from Janssen in 2019. The Company received a $5.0 million payment triggered by the successful nomination of a second-generation oral Interleukin ("IL")-23 receptor antagonist development compound ("second-generation compound") during the first quarter of 2020 and a $7.5 million payment triggered by the completion of data collection activities for the first Phase 1 clinical trial of a second-generation compound during the fourth quarter of 2021. The Company received a $25.0 million milestone payment in connection with the dosing of the third patient in the first Phase 2 clinical trial for a second-generation compound during the second quarter of 2022.

The Restated Agreement relates to the development, manufacture and commercialization of oral IL-23 receptor antagonist drug candidates. The candidates nominated for initial development pursuant to the Restated Agreement included PTG-200 (JNJ-67864238), PN-232 (JNJ-75105186) and JNJ-2113 (JNJ-77242113) (formerly known as PN-235). PTG-200 is an oral IL-23 receptor antagonist that was in Phase 2a development for the treatment of Crohn's disease ("CD"). During the fourth quarter of 2021, following a pre-specified interim analysis criteria, a portfolio decision was made by Janssen to stop further development of both PTG-200 and PN-232 in favor of advancing JNJ-2113, based on its superior potency and overall pharmacokinetic and pharmacodynamic profile. Janssen is primarily responsible for the conduct of all future trials, including current and anticipated Phase 2 trials, and the Company is primarily responsible for the conduct of the second-generation Phase 1 trials.

Pursuant to the Restated Agreement, the parties:

- amended development milestones to reflect Janssen's expected development of collaboration compounds for multiple indications in the IL-23 pathway;

- limited the Company's further development and related expense obligations under the Restated Agreement to the PTG-200 Phase 2a trial and the ongoing Phase 1 trials in PN-232 and JNJ-2113; Janssen is responsible for all other future development and related expenses under the Restated Agreement; and

- concluded the parties' two-year research collaboration, while enabling Janssen to continue conducting additional research through July 2024 on compounds developed pursuant to the Original Agreement.

The Restated Agreement enables Janssen to develop collaboration compounds for multiple indications. Under the Restated Agreement, Janssen is required to use commercially reasonable efforts to develop at least one collaboration compound for at least two indications.

The Company's development cost obligations in the Original Agreement for the period following the effective date of the Original Agreement were as follows: (a) up to $20.0 million of costs related to up to three Phase 1 trials of second-generation compounds; (b) up to $20.0 million of costs related to Phase 2a and 2b costs for PTG-200 (i.e., 20% of the first $100.0 million in costs); and (c) up to $25.0 million in costs related to up to two Phase 2 trials evaluating second-generation compounds.

The Company's development cost obligations under the Restated Agreement are as follows: (a) the Company funded 20% of the costs related to the Phase 2a trial evaluating PTG-200 for the treatment of CD (subject to a $20.0 million cap); (b) the Company was responsible for 50% of agreed-upon costs related to the Phase 1 trial evaluating JNJ-2113 incurred through January 4, 2021; and (c) the Company was responsible for 100% of agreed-upon costs related to the Phase 1 trial evaluating PN-232.

Certain of the Company's previous development cost obligations under the Original Agreement were limited or eliminated as follows: (a) the Company's previous $25.0 million obligation for 20% of costs related to Phase 2 trials for second-generation products was eliminated; (b) the Company's previous $5.0 million obligation for 50% of the costs of a potential third Phase 1 trial evaluating a second-generation compound was eliminated; and (c) the Company had no obligation to fund any portion of any Phase 2b or other trial evaluating PTG-200 beyond the Phase 2a trial in CD.

One milestone for second-generation Phase 2 development was reduced from $50.0 million to $25.0 million in the Restated Agreement; otherwise, the various milestone payment amounts in the Restated Agreement remain substantially the same as in the Original Agreement. To reflect parallel development of multiple indications in the IL-23 pathway, milestone payments under the Restated Agreement generally correspond to the achievement of specified milestones in: (a) any initial indication (rather than CD, as in the Original Agreement); (b) any second indication (rather than ulcerative colitis ("UC"), as in the Original Agreement); and (c) any third indication. With respect to second-generation compounds, milestone payments for second and third indications may be triggered by any second-generation compound (i.e., not necessarily the second-generation compound that triggered the initial payment for any indication, or the payment for a second indication). In addition, the opt-in payments contemplated by the Original Agreement related to the scope of Janssen's license rights have been converted into development milestones in the Restated Agreement.

Upcoming potential development milestones for second-generation compounds include:

- $10.0 million upon the dosing of the third patient in the first Phase 2 clinical trial for any second-generation compound for a second indication (i.e., an indication different than the indication which triggered the $25.0 million milestone received during the first quarter of 2022 described above);

- $50.0 million upon the dosing of the third patient in a Phase 3 clinical trial for a second-generation compound for any indication;

- $15.0 million upon the dosing of the third patient in a Phase 3 clinical trial for a second-generation compound for a second indication; and

- $115.0 million upon a Phase 3 clinical trial for a second-generation compound for any indication meeting its primary clinical endpoint.

Development milestones for PTG-200 were unchanged under the Restated Amendment, except that milestone achievement is generally no longer indication-specific.

Pursuant to the Restated Agreement, the Company remains eligible to receive tiered royalties on net product sales at percentages ranging from mid-single digits to ten percent. The sales milestone payments in the Original Agreement also remain the same in the Restated Agreement.

Pursuant to both the Original and Restated Agreements, payments to the Company for research and development services are generally billed and collected as services are performed or assets are delivered, including research activities and Phase 1 and Phase 2 development activities. Janssen bills the Company for its share of the PTG-200 Phase 2a development costs as expenses are incurred by Janssen. Milestone payments are received after the related milestones are achieved.

Janssen retains exclusive, worldwide rights to develop and commercialize IL-23 receptor antagonist compounds derived from the research collaboration conducted under the Original Agreement, or Janssen's further research under the Restated Agreement. Any further research and development will be conducted by Janssen. The Company will have the right to co-detail (for CD and UC indications) up to two of the IL-23 receptor antagonist compounds under the collaboration in the U.S. market.

The Restated Agreement remains in effect until the royalty obligations cease following patent and regulatory expiry, unless terminated earlier. Upon a termination of the Restated Agreement, all rights revert back to the Company, and in certain circumstances, if such termination occurs during ongoing clinical trials, Janssen would, if requested, provide certain financial and operational support to the Company for the completion of such trials.

Revenue Recognition

The Restated Agreement contains a single performance obligation for the development license; Phase 1 development services for PTG-200, PN-232 and JNJ-2113 (formerly known as PN-235); the Company's services associated with Phase 2a development for PTG-200 in CD; the initial year of second-generation compound research services; and all other such services that the Company may perform at the request of Janssen to support the development of PTG-200 through Phase 2a and PN-232 and JNJ-2113 through Phase 1. Under the Restated Agreement, development services performed by the Company for PTG-200 beyond Phase 2a and PN-232 and JNJ-2113 beyond Phase 1 are no longer required.

The Company determined that the license was not distinct from the revised development services within the context of the agreement because the revised development services did not change the utility of the intellectual property. The Company also concluded that the remaining development services are not distinct from the partially delivered combined promise comprised under the agreement prior to the Restated Agreement of the development license and PTG-200, PN-232 and JNJ-2113 services, including compound supply and other services. Therefore, the Restated Agreement is treated as if it were part of the Original Agreement. The Restated Agreement was accounted for as if it were a modification of services under the Original Agreement by applying a cumulative catch-up adjustment to revenue. As of the effective date of the Restated Agreement, the Company calculated the adjusted cumulative revenue under the Restated Agreement with primary updates to the transaction price, including the release of and update of prior constraints and fewer remaining services to be provided, resulting in a cumulative adjustment that increased revenue by $8.0 million for the year ended December 31, 2021.

The contract duration is defined as the period in which parties to the contract have present enforceable rights and obligations. For revenue recognition purposes, the duration of the Restated Agreement for the identified single initial performance obligations began on the Original Agreement effective date of July 13, 2017 and ended upon the completion of Phase 1 clinical trials for PN-232 and JNJ-2113. Final activities related to these trials were completed as of June 30, 2022.

The Company uses the most likely amount method to estimate variable consideration included in the transaction price. Variable consideration after the effective date of the Restated Agreement consisted of future milestone payments and cost sharing payments for agreed-upon services offset by development cost reimbursable to Janssen. Cost sharing payments from Janssen relate to the agreed-upon services for development activities that the Company performs within the duration of the contract and are included in the transaction price at the Company's share of estimated budgeted costs

for these activities, including primarily internal full-time equivalent effort and third-party contract costs. Cost sharing payments to Janssen relate to agreed-upon services for activities that Janssen performs within the duration of the contract are not a distinct service that Janssen transfers to the Company. Therefore, the consideration payable to Janssen is accounted for as a reduction in the transaction price.

The transaction price of the initial performance obligation under the Restated Agreement was $131.7 million as of December 31, 2022, an increase of $25.2 million from the transaction price of $106.5 million at December 31, 2021 under the Restated Agreement and an increase of $33.1 million from the transaction price of $98.6 million at December 31, 2020 under the Original Agreement. In order to determine the transaction price, the Company evaluates all payments to be received during the duration of the contract, net of development costs reimbursement expected to be payable to Janssen. The transaction price as of December 31, 2022 includes $112.5 million of nonrefundable payments received to date, $17.9 million of reimbursement from Janssen for services performed for IL-23 receptor antagonist compound research and other services, and variable consideration consisting of $8.2 million of development cost reimbursement from Janssen, partially offset by $6.9 million of net cost reimbursement due to Janssen for services performed. The Company concluded that the variable consideration constraint is appropriately reflected in the transaction price as of December 31, 2022, and that the achievement of future milestones is subject to additional development and/or regulatory uncertainty and therefore it is not probable at December 31, 2022 that a material reversal of such revenues will not occur. Janssen also opted in for certain additional services to be performed by the Company that were outside the initial performance obligation. Revenue for these additional services was recognized as these services were performed.

The Company utilized a cost-based input method to measure proportional performance and to calculate the corresponding amount of revenue to recognize. In applying the cost-based input method of revenue recognition, the Company used actual costs incurred relative to expected costs to fulfill the combined performance obligation. These costs consist primarily of internal full-time equivalent effort and third-party contract costs. Revenue was recognized based on actual costs incurred as a percentage of total estimated costs as the Company completed its performance obligations. A cost-based input method of revenue recognition requires management to make estimates of costs to complete the Company's performance obligations. The Company believes this is the best measure of progress because other measures do not reflect how the Company transfers its performance obligation to Janssen.

For the year ended December 31, 2022, the Company recognized $26.6 million of license and collaboration revenue, which was primarily related to the transaction price under the Restated Agreement recognized based on proportional performance. The Company completed its performance obligation under the collaboration as of June 30, 2022.

For the year ended December 31, 2021, the Company recognized $27.4 million of license and collaboration revenue. This amount included a cumulative catch-up adjustment increasing license and collaboration revenue by $8.0 million, and $18.6 million of license and collaboration revenue based on proportional performance following the Restated Agreement. In addition, the Company recorded $0.8 million of revenue related to additional services provided by the Company under the Restated Agreement.

For the year ended December 31, 2020, the Company recognized $28.6 million of license and collaboration revenue. This amount included $27.1 million of the transaction price based on proportional performance and an update in forecasted amounts for future services remaining to be performed and recognized under the Original Agreement. In addition, the Company recorded $1.5 million of revenue for the year ended December 31, 2020 related to additional services provided by the Company under the Original Agreement.

The following tables present changes in the Company's contract assets and liabilities during the periods presented (in thousands):

Year Ended December 31, 2022	Balance at Beginning of Period	Additions	Deductions	Balance at End of Period
Contract assets:				
Receivable from collaboration partner—related party	$ 1,566	$ 25,165	$ (26,721)	$ 10
Contract liabilities:				
Deferred revenue—related party	$ 1,601	$ 25,757	$ (27,358)	$ —
Payable to collaboration partner—related party	$ 899	$ 439	$ (1,269)	$ 69

Year Ended December 31, 2021	Balance at Beginning of Period	Additions	Deductions	Balance at End of Period
Contract assets:				
Receivable from collaboration partner—related party	$ 2,426	$ 14,056	$ (14,916)	$ 1,566
Contract liabilities:				
Deferred revenue—related party	$ 14,477	$ 25,141	$ (38,017)	$ 1,601
Payable to collaboration partner—related party	$ 2,732	$ 10,225	$ (12,058)	$ 899

During the year ended December 31, 2022, the Company recognized revenue of $0.9 million from amounts included in the deferred revenue balance at the beginning of the year. During the year ended December 31, 2021, the Company recognized revenue of $2.8 million from amounts included in the deferred revenue balance at the beginning of the year. During the year ended December 31, 2020, the Company recognized $14.1 million from amounts included in the deferred revenue balance at the beginning of the year. None of the costs to obtain or fulfill the contract were capitalized.

Note 4. Fair Value Measurements

Financial assets and liabilities are recorded at fair value. The accounting guidance for fair value provides a framework for measuring fair value, clarifies the definition of fair value and expands disclosures regarding fair value measurements. Fair value is defined as the price that would be received to sell an asset or paid to transfer a liability (an exit price) in an orderly transaction between market participants at the reporting date. The accounting guidance establishes a three-tiered hierarchy, which prioritizes the inputs used in the valuation methodologies in measuring fair value as follows:

Level 1—Inputs are unadjusted quoted prices in active markets for identical assets or liabilities at the measurement date.

Level 2—Inputs (other than quoted market prices included in Level 1) are either directly or indirectly observable for the asset or liability through correlation with market data at the measurement date and for the duration of the instrument's anticipated life.

Level 3—Inputs reflect management's best estimate of what market participants would use in pricing the asset or liability at the measurement date. Consideration is given to the risk inherent in the valuation technique and the risk inherent in the inputs to the model.

In determining fair value, the Company utilizes quoted market prices, broker or dealer quotations, or valuation techniques that maximize the use of observable inputs and minimize the use of unobservable inputs to the extent possible and considers counterparty credit risk in its assessment of fair value.

The following tables present the fair value of the Company's financial assets determined using the inputs defined above (in thousands).

	December 31, 2022			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$ 54,292	$ —	$ —	$ 54,292
Commercial paper	—	110,227	—	110,227
Corporate debt securities	—	10,741	—	10,741
U.S. Treasury and agency securities	—	57,242	—	57,242
Total financial assets	$ 54,292	$ 178,210	$ —	$ 232,502

	December 31, 2021			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$ 39,854	$ —	$ —	$ 39,854
Commercial paper	—	157,141	—	157,141
Corporate debt securities	—	75,548	—	75,548
U.S. Treasury and agency securities		40,017	—	40,017
Supranational and sovereign government securities	—	6,010	—	6,010
Total financial assets	$ 39,854	$ 278,716	$ —	$ 318,570

The Company's commercial paper, corporate debt securities, U.S. Treasury and agency securities, including U.S. Treasury bills, and supranational and sovereign government securities are classified as Level 2 as they were valued based upon quoted market prices for similar instruments in active markets, quoted prices for identical or similar instruments in markets that are not active and model-based valuation techniques, for which all significant inputs are observable in the market or can be corroborated by observable market data for substantially the full term of the assets.

The carrying amount of the Company's remaining financial assets and liabilities, including cash, receivables and payables, approximates their fair value due to their short-term nature.

Note 5. Cash Equivalents and Marketable Securities

Cash equivalents and marketable securities consisted of the following (in thousands):

	December 31, 2022			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Money market funds	$ 54,292	$ —	$ —	$ 54,292
Commercial paper	110,257	—	(30)	110,227
Corporate debt securities	10,756	—	(15)	10,741
U.S. Treasury and agency securities	57,251	27	(36)	57,242
Total cash equivalents and marketable securities	$ 232,556	$ 27	$ (81)	$ 232,502
Classified as:				
Cash equivalents				$ 120,891
Marketable securities				111,611
Total cash equivalents and marketable securities				$ 232,502

	December 31, 2021			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Money market funds	$ 39,854	$ —	$ —	$ 39,854
Commercial paper	157,157	—	(16)	157,141
Corporate debt securities	75,598	—	(50)	75,548
U.S. Treasury and agency securities	40,093	—	(76)	40,017
Supranational and sovereign government securities	6,011	—	(1)	6,010
Total cash equivalents and marketable securities	$ 318,713	$ —	$ (143)	$ 318,570
Classified as:				
Cash equivalents				$ 115,335
Marketable securities				203,235
Total cash equivalents and marketable securities				$ 318,570

Marketable securities of $111.6 million and $203.2 million held as of December 31, 2022 and 2021, respectively, had contractual maturities of less than one year. The Company does not intend to sell its securities that are in an unrealized loss position, and it is not more likely than not that the Company will be required to sell its securities before recovery of their amortized cost basis, which may be at maturity. Factors considered in determining whether a loss is temporary include the length of time and extent to which the fair value has been less than the amortized cost basis and whether the Company intends to sell the security or whether it is more likely than not that the Company would be required to sell the security before recovery of the amortized cost basis. There were no realized gains or realized losses on marketable securities for the periods presented.

Note 6. Balance Sheet Components

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consisted of the following (in thousands):

	December 31,	
	2022	2021
Prepaid clinical and research related expenses	$ 2,746	$ 5,242
Prepaid insurance	1,417	1,746
Other prepaid expenses	1,507	1,515
Other receivable	42	975
Prepaid expenses and other current assets	$ 5,712	$ 9,478

Property and Equipment, Net

Property and equipment, net consisted of the following (in thousands):

	December 31,	
	2022	2021
Laboratory equipment	$ 4,817	$ 4,156
Furniture and computer equipment	1,089	1,023
Leasehold improvements	913	877
Total property and equipment	6,819	6,056
Accumulated depreciation	(5,254)	(4,258)
Property and equipment, net	$ 1,565	$ 1,798

Depreciation expense for the years ended December 31, 2022, 2021 and 2020, was $1,032,000, $813,000 and $789,000, respectively. As of December 31, 2022, 2021 and 2020, $156,000, $262,000 and $46,000, respectively, of property and equipment, net, was located in Australia. The remainder of the Company's property and equipment, net is located in the United States.

Accrued Expenses and Other Payables

Accrued expenses and other payables consisted of the following (in thousands):

	December 31,	
	2022	2021
Accrued clinical and research related expenses	$ 19,109	$ 27,950
Accrued employee related expenses	4,967	7,125
Accrued professional service fees	464	734
Accrued payment to former collaboration partner	—	1,500
Other	415	407
Total accrued expenses and other payables	$ 24,955	$ 37,716

Note 7. Research Collaboration and License Agreement

The Company and Zealand Pharma A/S entered into a collaboration agreement in June 2012. In October 2013, Zealand Pharma abandoned the collaboration, and the collaboration agreement was terminated in 2014. The agreement provides for certain post-termination payment obligations to Zealand with respect to compounds related to the collaboration that meet specified conditions set forth in the collaboration agreement and which the Company elects to further develop following Zealand's abandonment of the collaboration. The Company has the right, but not the obligation, to further develop and commercialize such compounds. The agreement provides for payments to Zealand for the achievement of certain development, regulatory and sales milestone events that occur prior to a partnering arrangement related to such compounds between the Company and a third party.

The Company previously determined that rusfertide is a compound for which the post-termination payments described above are required under the collaboration agreement and has made three development milestone payments for an aggregate amount of $1.0 million under the agreement. However, upon reevaluation, the Company concluded in 2019 that rusfertide is not a compound requiring post-termination payments under the agreement and initiated an arbitration proceeding in January 2020. On August 4, 2021, the Company and Zealand agreed to resolve the dispute and entered into an Arbitration Resolution Agreement.

See Note 11. Commitments and Contingencies—Legal Proceedings for additional information on the results of arbitration proceedings related to this research and collaboration agreement.

Milestone payments to collaboration partners are recorded as research and development expense in the period that the expense is incurred. For the year ended December 31, 2021, the Company recorded research and development expense of $4.0 million under this agreement. No research and development expense was recorded under this agreement for the years ended December 31, 2022 or 2020.

Note 8. Research and Development Tax Incentive

Research and Development Tax Incentive

The Company did not recognize any research and development cash tax incentive from the Australian Tax Office ("ATO") during the year ended December 31, 2022. During the years ended December 31, 2021 and 2020, the Company recognized AUD 4.2 million ($3.1 million) and AUD 1.4 million ($1.0 million), respectively, as a reduction of research and development expenses in connection with the research and development cash tax incentive from the ATO. As of December 31, 2021 and 2020, the research and development tax incentive receivable was AUD 3.8 million ($2.8 million) and AUD 1.4 million ($1.1 million), respectively. There was no cash tax incentive receivable balance as of December 31, 2022.

Note 9. Term Loan Facility

On October 30, 2019 (the "Closing Date"), the Company entered into a Credit and Security Agreement, by and among the Company, MidCap Financial Trust, as a lender, Silicon Valley Bank, as a lender, the other lenders party thereto from time to time and MidCap Financial Trust, as administrative agent and collateral agent ("Agent"), (the "Term Loan Credit Agreement"), which provided for a $50.0 million term loan facility. The Term Loan Credit Agreement provided for (i) on the Closing Date, $10.0 million aggregate principal amount of term loans, (ii) at the Company's option until December 31, 2020, an additional $20.0 million term loan facility subject to the satisfaction of certain conditions, including clinical milestone achievement, and (iii) at the Company's option, until September 30, 2021, an additional $20.0 million term loan facility subject to the satisfaction of certain conditions, including clinical milestone achievement, (collectively, the "Term Loans"). The Company intended to use any proceeds of the Term Loans for general corporate purposes.

In June 2020, the Company prepaid its outstanding $10.0 million balance on the term loan as well as $0.6 million for related prepayment and exit fees. Accordingly, the company accelerated amortization of $0.1 million related to capitalized and unamortized debt issuance costs, which is included as part of the $0.6 million loss on early repayment of debt. The Company did not exercise its option to borrow the $20.0 million second tranche of Term Loans, which expired on December 31, 2020. In September 2021, the Company executed a payoff letter to release all obligations under the Term Loan Credit Agreement, ending the Term Loan Credit Agreement. The Company had no outstanding balance as of December 31, 2022, 2021 or 2020 related to the Term Loan Credit Agreement.

The Company recognized $0.6 million in interest expense related to the Term Loans during the year ended December 31, 2020. No interest expense related to the Term Loans was recognized during the years ended December 31, 2022 and 2021. The Company accounts for interest on its long-term debt under the effective interest method, with interest expense comprised of contractual interest, amortization of origination fees and other issuance costs, and accretion of final payment fees.

Note 10. Leases

The Company applies ASC 842 to recognize assets and liabilities for leases with lease terms of more than 12 months on the balance sheet. The Company has elected to account for each separate lease component and non-lease components as one single component for all lease assets. Leases with terms of 12 months or less are not recorded on the balance sheet, and the related lease expenses are recognized on a straight-line basis over the lease term.

The Company has one operating lease agreement originally entered into in March 2017 for approximately 42,900 square feet for laboratory and office space located in Newark, California. On July 2, 2021, the Company entered into a second amendment to its original facility lease agreement, as amended, for 15,000 square feet of additional office space in Newark, California (the "Second Amendment"). The Company commenced operations in the additional space in September 2021. Under the Second Amendment, the Company will pay additional base rent of approximately $1.5 million over the lease term, which expires in May 2024. As a result of this amendment, the Company recorded an additional right-of-use-asset and the related liability of $1.4 million as of December 31, 2021.

The Company provided the landlord with a $450,000 letter of credit collateralized by restricted cash as security deposit for the operating lease agreement, which expires in May 2024. The security deposit for the lease was later reduced to $225,000 in March 2021. No additional security deposit was required pursuant to the Second Amendment. Under the terms of the lease, as amended, the Company is responsible for its proportional share of operating expenses and tax obligations.

Balance sheet information related to operating leases is as follows for the periods presented (in thousands):

	December 31,	
Operating Leases:	**2022**	**2021**
Operating lease right-of-use asset	$ 3,061	$ 4,936
Operating lease liability—current	$ 2,515	$ 2,200
Operating lease liability—noncurrent	1,141	3,658
Total operating lease liabilities	$ 3,656	$ 5,858
Weighted-average remaining lease term (years)	1.4	2.4
Weighted-average discount rate	10.4%	10.4%

Other information related to the Company's operating leases is as follows for the periods presented (in thousands):

	Year Ended December 31,		
	2022	**2021**	**2020**
Operating lease cost	$ 2,335	$ 1,962	$ 1,775
Less: Sublease income	(123)	(91)	(89)
Total lease expense	$ 2,212	$ 1,871	$ 1,686

Supplemental cash flow information is as follows for the periods presented (in thousands):

	Year Ended December 31,		
	2022	**2021**	**2020**
Operating cash flow used by operating leases	$ 2,661	$ 2,049	$ 1,941
New operating lease asset obtained in exchange for operating lease liability	$ —	$ 1,373	$ —

Future lease payments required under lease obligations as of December 31, 2022 are as follows (in thousands):

Year Ending December 31:	**Amount**
2023	$ 2,743
2024	1,161
2025	—
2026	—
Thereafter	—
Total future minimum lease payments	3,904
Less: imputed interest	(248)
Present value of lease liabilities	$ 3,656

Note 11. Commitments and Contingencies

Contract Service Providers

In the normal course of business, the Company enters into agreements with contract service providers to assist in the performance of its research and development activities and clinical and commercial manufacturing activities. Subject to required notice periods and the Company's obligations under binding purchase orders, the Company can elect to discontinue the work under these agreements at any time. The Company expects to enter into additional clinical development, contract research, clinical and commercial manufacturing, supplier and collaborative research agreements in the future, which may require upfront payments and long-term commitments of capital resources.

Indemnification Agreements

In the ordinary course of business, the Company enters into agreements that may include indemnification provisions. Pursuant to such agreements, the Company may indemnify, hold harmless and defend an indemnified party for losses suffered or incurred by the indemnified party. Some of the provisions will limit losses to those arising from third-party actions. In some cases, the indemnification will continue after the termination of the agreement. The maximum potential amount of future payments the Company could be required to make under these provisions is not determinable. The Company has also entered into indemnification agreements with its directors and officers that may require the Company to indemnify its directors and officers against liabilities that may arise by reason of their status or service as directors or officers to the fullest extent permitted by law. The Company carries a directors' and officers' insurance policy. To date, the Company has not incurred material costs to defend lawsuits or settle claims related to the indemnification agreements. The Company believes that the fair value of these indemnification agreements is minimal and has not accrued any amounts for the obligations.

Legal Proceedings

The Company recognizes accruals for legal actions to the extent that it concludes that a loss is both probable and reasonably estimable. The Company accrues for the best estimate of a loss within a range; however, if no estimate in the range is better than any other, it accrues the minimum amount in the range. If the Company determines that a loss is reasonably possible and the loss or range of loss can be estimated, it discloses the possible loss.

On January 23, 2020, the Company initiated arbitration proceedings with the International Court of Arbitration of the International Chamber of Commerce against Zealand Pharma A/S ("Zealand") related to a collaboration agreement the Company and Zealand entered into in 2012 and terminated in 2014. The agreement provides for certain post-termination payment obligations to Zealand with respect to compounds related to the collaboration that the Company elects to further develop and meet specified conditions.

On August 4, 2021, the Company and Zealand agreed to resolve the dispute and reached an Arbitration Resolution Agreement. Under the Arbitration Resolution Agreement, (1) the Company was required to make an additional payment of $1.5 million to Zealand in August 2022 with respect to rusfertide; (2) all development milestones with respect of rusfertide were reduced by 50%, except that the Company agreed to pay in full within two business days after the effective date of the Arbitration Resolution Agreement (and timely paid): (i) a $1.0 million milestone for initiation of a Phase 2b clinical trial; and (ii) a $1.5 million milestone for initiation of a Phase 3 clinical trial; (3) the royalty rates payable by the Company on net sales of rusfertide were reduced by 50%; (4) all sales milestone payments on net sales of rusfertide were reduced by 50%; (5) the parties agreed that each party will retain all payments previously made by the other party in connection with the original collaboration agreement; and (6) the parties released claims related to the original collaboration agreement, the abandonment agreement and the arbitration. In addition to the payments specified in items (1) and (2) above, the Company may also be required to pay Zealand up to $2.75 million in future development milestone payments relating to rusfertide. Those payments include up to $1.0 million in the aggregate for registrational proposals and up to $1.75 million in the aggregate for commercial launch in the three geographic territories specified in the original collaboration agreement.

The Company considered the outcome of these arbitration proceedings as being related to its research and development project; therefore, payments or milestone payments were recorded as research and development expenses.

Note 12. Stockholders' Equity

In August 2018, the Company entered into a Securities Purchase Agreement with certain accredited investors (each, an "Investor" and, collectively, the "Investors"), pursuant to which the Company sold an aggregate of 2,750,000 shares of its common stock at a price of $8.00 per share, for aggregate net proceeds of $21.7 million, after deducting offering expenses payable by the Company. In a concurrent private placement, the Company issued the Investors warrants to purchase an aggregate of 2,750,000 shares of its common stock (each, a "Warrant" and, collectively, the "Warrants"). Each Warrant is exercisable from August 8, 2018 through August 8, 2023. Warrants to purchase 1,375,000 shares of the Company's common stock have an exercise price of $10.00 per share and Warrants to purchase 1,375,000 shares of the

Company's common stock have an exercise price of $15.00 per share. The exercise price and number of shares of common stock issuable upon the exercise of the Warrants (the "Warrant Shares") are subject to adjustment in the event of any stock dividends and splits, reverse stock split, recapitalization, reorganization or similar transaction, as described in the Warrants. Under certain circumstances, the Warrants may be exercisable on a "cashless" basis. In connection with the issuance and sale of the common stock and Warrants, the Company granted the Investors certain registration rights with respect to the Warrants and the Warrant Shares. The common stock and warrants are classified as equity in accordance with Accounting Standards Codification Topic 480*, Distinguishing Liabilities from Equity* ("ASC 480")*,* and the net proceeds from the transaction were recorded as a credit to additional paid-in capital. As of December 31, 2022, none of the Warrants have been exercised.

In December 2018, the Company entered into an exchange agreement (the "Exchange Agreement") with an Investor and its affiliates (the "Exchanging Stockholders"), pursuant to which the Company exchanged an aggregate of 1,000,000 shares of the Company's common stock, par value $0.00001 per share, owned by the Exchanging Stockholders for pre-funded warrants (the "Exchange Warrants") to purchase an aggregate of 1,000,000 shares of common stock (subject to adjustment in the event of any stock dividends and splits, reverse stock split, recapitalization, reorganization or similar transaction, as described in the Exchange Warrants), with an exercise price of $0.00001 per share. The Exchange Warrants expire ten years from the date of issuance. The Exchange Warrants were exercisable at any time prior to expiration except that the Exchange Warrants could not be exercised by the Exchanging Stockholders if, after giving effect thereto, the Exchanging Stockholders would beneficially own more than 9.99% of the Company's common stock, subject to certain exceptions. In accordance with Accounting Standards Codification Topic 505, *Equity*, the Company recorded the retirement of the common stock exchanged as a reduction of common stock shares outstanding and a corresponding debit to additional paid-in-capital at the fair value of the Exchange Warrants on the issuance date. The Exchange Warrants were classified as equity in accordance with ASC 480*,* and the fair value of the Exchange Warrants was recorded as a credit to additional paid-in capital and is not subject to remeasurement. The Company determined that the fair value of the Exchange Warrants was substantially similar to the fair value of the retired shares on the issuance date due to the negligible exercise price for the Exchange Warrants. During the year ended December 31, 2019, Exchange Warrants to purchase 600,000 shares of the Company's common stock were net exercised, resulting in the issuance of 599,997 shares of common stock. During the year ended December 31 2022, Exchange Warrants to purchase 400,000 shares of the Company's common stock were net exercised, resulting in the issuance of 399,997 shares of common stock. As of December 31, 2022, there were no outstanding Exchange Warrants.

In November 2019, the Company entered into an Open Market Sale Agreement℠ (the "Prior Sales Agreement"), pursuant to which the Company could offer and sell up to $75.0 million of shares of common stock from time to time in "at-the-market" offerings (the "2019 ATM Facility"). During the year ended December 31, 2020, the Company sold 2,483,719 shares of its common stock under the 2019 ATM Facility for net proceeds of $41.9 million, after deducting issuance costs. No shares were sold under the 2019 ATM Facility during the year ended December 31, 2021. During the year ended December 31, 2022, the Company sold 422,367 shares of its common stock under the 2019 ATM Facility for net proceeds of $14.6 million, after deducting issuance costs. The Prior Sales Agreement was terminated in connection with and replaced by the Sales Agreement in August 2022.

In May 2020, the Company completed an underwritten public offering of 7,000,000 shares of common stock at a public offering price of $14.00 per share and issued an additional 1,050,000 shares of its common stock at a price of $14.00 per share following the underwriters' exercise of their option to purchase additional shares. Net proceeds, after deducting underwriting commissions and offering costs paid by the Company, were $105.3 million.

In December 2020, the Company completed an underwritten public offering of 4,761,904 shares of common stock at a public offering price of $21.00 per share and issued an additional 714,285 shares of its common stock at a price of $21.00 per share following the underwriters' exercise of their option to purchase additional shares. Net proceeds, after deducting underwriting commissions and offering costs paid by the Company, were $107.6 million.

In June 2021, the Company completed an underwritten public offering of 3,046,358 shares of its common stock at a public offering price of $37.75 per share and issued an additional 456,953 shares of common stock at a price of $37.75 per share following the underwriters' exercise of their option to purchase additional shares. Net proceeds, after deducting underwriting commissions and offering costs paid by the Company, were $123.8 million.

In August 2022, the Company entered into an Open Market Sale Agreement℠ (the "Sales Agreement"), pursuant to which the Company may offer and sell up to $100.0 million of shares of its common stock from time to time in "at-the-market" offerings (the "2022 ATM Facility"). As of December 31, 2022, no sales were made under the 2022 ATM Facility.

Note 13. Equity Plans

Equity Incentive Plan

In May 2007, the Company established the 2007 Stock Option and Incentive Plan ("2007 Plan") which provided for the granting of stock options to employees and consultants of the Company. Options granted under the 2007 Plan were either incentive stock options ("ISOs") or nonqualified stock options ("NSOs"). ISOs were granted only to Company employees. NSOs were granted to Company employees, non-employee board directors and consultants. Options under the 2007 Plan have a term of ten years and generally vest over a four-year period.

In July 2016, the Company's board of directors and stockholders approved the 2016 Equity Incentive Plan ("2016 Plan") to replace the 2007 Plan. Under the 2016 Plan, 1,200,000 shares of the Company's common stock were initially reserved for the issuance of stock options, restricted stock units and other awards to employees, directors and consultants. Pursuant to the "evergreen" provision contained in the 2016 Plan, the number of shares reserved for issuance under the 2016 Plan automatically increases on January 1 of each year, starting on January 1, 2017 and continuing through (and including) January 1, 2026, by 4% of the total number of shares of the Company's capital stock outstanding on December 31 of the preceding fiscal year, or a lesser number of shares determined by the Company's board of directors. Upon adoption of the 2016 Plan, no additional stock awards were issued under the 2007 Plan. Options granted under the 2007 Plan that were outstanding on the date the 2016 Plan became effective remain subject to the terms of the 2007 Plan. The number of options available for grant under the 2007 Plan was ceased and the number was added to the common stock reserved for issuance under the 2016 Plan. As of December 31, 2022, approximately 1,350,793 shares of common stock were available for issuance under the 2016 Plan.

The 2016 Plan is administered by the board of directors, or a committee appointed by the board of directors, which determines the types of awards to be granted, including the number of shares subject to the awards, the exercise price and the vesting schedule. Options granted under the 2016 Plan expire no later than ten years from the date of grant. The exercise price of each option may not be less than 100% of the fair market value of the common stock at the date of grant. Options may be granted to stockholders possessing more than 10% of the total combined voting power of all classes of stocks of the Company at an exercise price at least 110% of the fair value of the common stock at the date of grant and the options are not exercisable after the expiration of 10 years from the date of grant. Employee stock options generally vest over a period of approximately four years. Non-employee director initial stock options generally vest monthly over a period of approximately three years, and non-employee director annual refresher stock options generally vest over a period of approximately one year.

Inducement Plan

In May 2018, the Company's board of directors approved the 2018 Inducement Plan, as subsequently amended. The 2018 Inducement Plan is a non-stockholder approved stock plan, under which awards options and restricted stock unit awards to persons that were not previously employees or directors of the Company, or following a bona fide period of non-employment, as an inducement material to such persons entering into employment with the Company, within the meaning of Rule 5635(c)(4) of the Nasdaq Listing Rules. The 2018 Inducement Plan is administered by the board of directors or the Compensation Committee of the board, which determines the types of awards to be granted, including the number of shares subject to the awards, the exercise price and the vesting schedule. Awards granted under the 2018 Inducement Plan expire no later than ten years from the date of grant. As of December 31, 2022, approximately 574,772 shares of common stock were available for issuance under the 2018 Inducement Plan, as amended.

Stock Options

Stock option activity under the Company's equity incentive and inducement plans is set forth below:

	Options Outstanding	Weighted-Average Exercise Price Per Share	Weighted-Average Remaining Contractual Life (years)	Aggregate Intrinsic Value (1) (in millions)
Balances at December 31, 2021	5,890,540	$ 17.66		
Options granted	1,763,300	22.39		
Options exercised	(519,113)	6.90		
Options forfeited	(894,218)	23.64		
Balances at December 31, 2022	6,240,509	$ 19.03	7.00	$ 6.9
Options exercisable—December 31, 2022	3,822,404	$ 16.90	5.92	$ 5.0
Options vested and expected to vest—December 31, 2022	6,240,509	$ 19.03	7.00	$ 6.9

(1) The aggregate intrinsic values were calculated as the difference between the exercise price of the options and the closing price of the Company's common stock on December 31, 2022. The calculation excludes options with an exercise price higher than the closing price of the Company's common stock on December 31, 2022.

The aggregate intrinsic value of options exercised was $5.4 million, $10.5 million and $3.0 million for the years ended December 31, 2022, 2021 and 2020, respectively.

During the years ended December 31, 2022, 2021 and 2020, the estimated weighted-average grant-date fair value of common stock underlying options granted was $17.52, $21.94 and $7.76 per share, respectively.

For the years ended December 31, 2022, 2021 and 2020, the aggregate fair value of stock options that vested during the year was $23.3 million, $11.3 million and $7.1 million, respectively.

Stock Options Valuation Assumptions

The fair value of stock option awards was estimated at the date of grant using a Black-Scholes option-pricing model with the following assumptions:

	Year Ended December 31,		
	2022	2021	2020
Expected term (in years)	5.27–6.08	5.27–6.08	5.27–6.08
Expected volatility	96.3%–101.7%	87.4%–95.2%	72.1%–87.5%
Risk-free interest rate	1.64%–4.23%	0.11%–1.35%	0.23%–1.44%
Dividend yield	—	—	—

In determining the fair value of the options granted, the Company uses the Black-Scholes option-pricing model and assumptions discussed below. Each of these inputs is subjective, and generally requires judgment to determine.

Expected Term—The Company's expected term represents the period that the Company's options granted are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term). The Company has limited historical exercise information to develop reasonable expectations about future exercise patterns and post-vesting employment termination behavior for its stock option grants.

Expected Volatility—For the year ended December 31, 2020, the Company's expected volatility was based upon a blend of 75% of the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants and 25% of the volatility of the Company's stock price since its initial public

offering in August 2016. For the year ended December 31, 2021, the Company's expected volatility was estimated based upon a mix of 50% of the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants and 50% of the volatility of the Company's stock price since its initial public offering in August 2016. For the year ended December 31, 2022, the Company's expected volatility was estimated based upon a mix of 25% of the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants and 75% of the volatility of the Company's stock price since its initial public offering in August 2016.

Risk-Free Interest Rate—The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of option.

Expected Dividend—The Company has never paid dividends on its common stock and has no plans to pay dividends on its common stock. Therefore, the Company used an expected dividend yield of zero.

Restricted Stock Units

A restricted stock unit award ("RSU") is an agreement to issue shares of the Company's common stock at the time of vesting. RSUs generally vest annually in equal installments over three or four years on approximately the anniversary of the grant date. RSUs granted to certain non-executive employees in 2022 vest 100% annually on approximately the first anniversary of the grant date. RSUs granted to certain executives in 2021 vest 100% on the third anniversary of the grant date.

RSU activity under the Company's equity incentive plans is set forth below:

	Number of Shares	Weighted Average Grant Date Fair Value
Unvested RSUs at December 31, 2021	405,972	$ 20.13
Granted	527,700	18.57
Vested	(108,462)	15.83
Forfeited	(187,774)	20.86
Unvested RSUs at December 31, 2022	637,436	$ 19.29

Stock-based compensation expense associated with RSUs is based on the fair value of the Company's common stock on the grant date, which equals the closing market price of the Company's common stock on the grant date. For RSUs, the Company recognizes compensation expense over the vesting period of the awards that are ultimately expected to vest.

For the years ended December 31, 2022, 2021 and 2020, the aggregate fair value of RSUs that vested during the year was $1.7 million, $0.8 million and $1.2 million, respectively.

Performance Stock Units

Performance stock unit award ("PSU") activity under the Company's equity incentive plans is set forth below:

	Number of Shares	Weighted Average Grant Date Fair Value
Unvested PSUs at December 31, 2021	105,500	$ 23.57
Granted	121,000	8.76
Vested	—	—
Forfeited	(27,000)	23.57
Unvested PSUs at December 31, 2022	199,500	$ 14.59

The terms of the unvested PSUs provide for 100% of shares to be earned based on the achievement of certain pre-determined performance objectives, subject to the participant's continued employment. The PSUs will vest, if at all, upon certification by the Compensation Committee of the Company's Board of Directors of the actual achievement of the performance objectives, subject to specified change of control exceptions.

Stock-based compensation expense associated with PSUs is based on the fair value of the Company's common stock on the grant date, which equals the closing price of the Company's common stock on the grant date. The Company recognizes compensation expense over the vesting period of the awards that are ultimately expected to vest when the achievement of the related performance objective becomes probable. The total fair value of grant date fair value of unvested PSUs outstanding as of December 31, 2022 was $2.9 million. As of December 31, 2022, the achievement of the related performance objectives was deemed not probable and, accordingly, no stock-based compensation expense for the unvested PSUs has been recognized as of December 31, 2022.

Employee Stock Purchase Plan

In July 2016, the Company's board of directors and stockholders approved the 2016 Employee Stock Purchase Plan ("2016 ESPP"). The 2016 ESPP is intended to qualify as an employee stock purchase plan under Section 423 of the Internal Revenue Code of 1986, as amended, and is administered by the Company's board of directors and the Compensation Committee of the board of directors. Under the 2016 ESPP, 150,000 shares of the Company's common stock were initially reserved for employee purchases of the Company's common stock. Pursuant to the "evergreen" provision contained in the 2016 ESPP, the number of shares reserved for issuance automatically increases on January 1 of each year, starting on January 1, 2017 and continuing through (and including) January 1, 2026 by the lesser of (i) 1% of the total number of shares of common stock outstanding on December 31 of the preceding fiscal year (ii) 300,000 shares, or (iii) such other number of shares determined by the board of directors.

The 2016 ESPP allows eligible employees to purchase shares of the Company's common stock at a discount through payroll deductions of up to 15% of their eligible compensation. At the end of each offering period, eligible employees are able to purchase shares at 85% of the lower of the fair market value of the Company's common stock at the beginning of the offering period or at the end of each applicable purchase period. During the year ended December 31, 2022, a total of 58,709 shares of common stock were issued under the 2016 ESPP, and approximately 1,255,290 shares of common stock were available for issuance as of December 31, 2022.

The fair value of the rights granted under the 2016 ESPP was calculated using the Black-Scholes option-pricing model with the following assumptions:

	Year Ended December 31,		
	2022	2021	2020
Expected term (in years)	0.50	0.50	0.50
Expected volatility	117.5%–128.2%	50.9%–69.7%	89.1%–120.4%
Risk-free interest rate	0.75%–3.56%	0.06%	0.12%–0.43%
Dividend yield	—	—	—

Stock-Based Compensation

Total stock-based compensation expense was as follows (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Research and development	$ 14,719	$ 8,996	$ 4,121
General and administrative	9,483	7,399	3,778
Total stock-based compensation expense	$ 24,202	$ 16,395	$ 7,899

As of December 31, 2022, total unrecognized stock-based compensation expense was approximately $47.6 million, which the Company expects to recognize over a weighted-average period of approximately 2.4 years.

Note 14. 401(k) Plan

The Company has a retirement and savings plan under Section of 401(k) of Internal Revenue Code (the "401(k) Plan") covering all U.S. employees. The 401(k) Plan allows employees to make pre- and post-tax contributions up to the maximum allowable amount set by the Internal Revenue Service. The Company may make contributions to this plan at its discretion. The Company matched 50% of each employee's contribution up to a maximum of $4,000 for the year ended December 31, 2022 and $3,500 for the year ended December 31, 2021, resulting in recognized expense of approximately $0.3 million for the years ended December 31, 2022 and 2021. No matching contributions were made to the plan by the Company for the year ended December 31, 2020.

Note 15. Income Taxes

No income tax expense was recorded by the Company for the years ended December 31, 2022, and 2021.

The Company recorded income tax expense of $1.3 million for the year ended December 31, 2020. During the second quarter of 2020, the Company's Australia subsidiary sold beneficial rights to discovery intellectual property to its U.S. entity, and the U.S. entity reimbursed the Australia subsidiary for certain direct development costs. Upon completion of the sale, the Company analyzed tax planning strategies and future income and concluded that a full valuation allowance is necessary for its Australia subsidiary. Income tax expense for the year ended December 31, 2020 reflects this sale of intellectual property rights, cost reimbursements and related adjustments to the deferred tax asset, establishing a valuation allowance and certain uncertain tax position liabilities. The Company's effective income tax rate differed from the Company's federal statutory rate of 21%, primarily because its U.S. loss cannot be benefited due to the full valuation position and reduced by foreign taxes.

The following table presents domestic and foreign components of net loss before income taxes (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Domestic	$ (124,208)	$ (125,797)	$ (71,073)
Foreign	(3,185)	246	6,228
Total net loss before taxes	$ (127,393)	$ (125,551)	$ (64,845)

The federal, state and foreign components of the income tax expense (benefit) are summarized as follows (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Current:			
Federal	$ —	$ —	$ —
State	—	—	—
Foreign	—	—	(88)
Total current tax (benefit) expense	—	—	(88)
Deferred:			
Federal	—	—	—
State	—	—	—
Foreign	—	—	1,393
Total deferred tax expense	—	—	1,393
Total income tax expense	$ —	$ —	$ 1,305

The effective tax rate of the provision for income taxes differs from the federal statutory rate as follows:

	Year Ended December 31,		
	2022	2021	2020
Federal statutory income tax rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal benefit	1.4	1.9	1.9
Research and development credits	5.9	4.3	6.5
Foreign tax rate difference	0.2	—	(0.9)
Change in valuation allowance	(25.8)	(28.0)	(34.3)
Other	(2.7)	0.8	3.8
Provision for income taxes	— %	— %	(2.0)%

The components of the deferred tax assets are as follows (in thousands):

	December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 76,133	$ 75,649
Depreciation and amortization	893	1,153
Accruals/other	8,304	5,716
Operating lease liability	769	1,230
Research and development and foreign credits	30,387	21,197
Section 174 capitalized R&D expenditure	22,296	—
Total deferred tax assets	138,782	104,945
Deferred tax liabilities:		
Operating right-of-use asset	(644)	(1,037)
Total deferred tax liabilities	(644)	(1,037)
Valuation allowance	(138,138)	(103,908)
Net deferred tax assets	$ —	$ —

ASC 740 requires that the tax benefit of net operating losses, temporary differences and credit carryforwards be recorded as an asset to the extent that management assesses that realization is “more likely than not”. Realization of the future tax benefits is dependent on the Company’s ability to generate sufficient taxable income within the carryforward period. Because of the Company’s recent history of operating losses, management believes that recognition of the deferred tax assets arising from the above-mentioned future tax benefits is currently not likely to be realized and, accordingly, has provided a valuation allowance. The valuation allowance increased by approximately $34.2 million, $32.0 million and $19.4 million during the years ended December 31, 2022, 2021 and 2020, respectively.

Federal and state laws impose substantial restrictions on the utilization of net operating loss and tax credit carryforwards in the event of an ownership change for tax purposes, as defined in Section 382 of the Internal Revenue Code. As a result of such ownership changes, the annual limitation may result in the expiration of net operating losses and credits before utilization. The Company performed a Section 382 analysis through December 31, 2022. The Company has experienced ownership changes in the past and in the current year. The ownership changes will not result in a limitation that will materially reduce the total amount of net operating loss carryforwards and credits that can be utilized. Subsequent ownership changes may affect the limitation in future years.

As of December 31, 2022, the Company had $349.5 million of federal net operating loss carryforwards and $214.8 million of state net operating loss carryforwards. $78.7 million of the federal net operating loss carryforwards will begin to expire in 2033, if not utilized, and the remaining $270.8 million have no expiration date. The state net operating loss carryforwards will begin to expire in 2035, if not utilized.

As of December 31, 2022, the Company had approximately AUD 0.3 million ($0.2 million) of Australian tax loss carryforward.

As of December 31, 2022, the Company had $28.1 million of federal and $10.7 million of state research and development tax credit carryforwards available to reduce future income taxes. The federal research and development tax credits will begin to expire in 2035, if not utilized. The state research and development tax credits have no expiration date.

As of December 31, 2022, the Company had AUD 4.4 million ($3.0 million) of Australian research and development tax credit carryforwards available to reduce future income taxes. The Australian research and development tax credits have no expiration date.

A reconciliation of the beginning and ending amount of unrecognized tax benefits is as follows (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Balance at beginning of year	$ 33,159	$ 19,885	$ 16,631
Decreases based on tax positions related to prior years	(10,779)	—	(3,799)
Increases based on tax positions related to current year	2,915	13,274	7,053
Balance at end of year	$ 25,295	$ 33,159	$ 19,885

At December 31, 2022, the Company had unrecognized tax benefits of $25.3 million, which are subject to a valuation allowance and would not affect the effective tax rate if recognized. The Company does not anticipate that the total amounts of unrecognized tax benefits will significantly increase or decrease in the next 12 months. The Company's policy is to include interest and penalties related to unrecognized tax benefits within the provision for income taxes, as necessary. Management determined that no accrual for interest or penalties was required as of December 31, 2022, 2021 and 2020.

The Company files income tax returns in the United States federal jurisdiction, the State of California, the State of Florida, and Australia. The Company is not currently under examination by income tax authorities in federal, state or other jurisdictions. The Company's tax returns remain open for examination for all years.

The Company's Australia subsidiary had an accumulated deficit at December 31, 2022 and, accordingly, no provision has been provided thereon for any unremitted earnings.

The Company has elected to recognize any potential global intangible low-taxed income ("GILTI") obligation as an expense in the period it is incurred.

The Company has received orphan drug designation from the U.S. Food and Drug Administration ("FDA") for its clinical asset rusfertide (PTG-300) for the treatment of polycythemia vera and beta-thalassemia and may qualify for a related 25% U.S. Federal income tax credit on qualifying clinical study expenditures.

Tax Law Updates

On December 22, 2017, the U.S. enacted comprehensive tax legislation (the "Tax Act"). The Tax Act made broad and complex changes to the U.S. tax code, including the imposition of a one-time mandatory deemed repatriation tax ("Transition Tax") on certain earnings accumulated offshore since 1986 and the reduction of the corporate tax rate from 35% to 21% for U.S. taxable income, resulting in a one-time remeasurement of U.S. federal deferred tax assets and liabilities. The Tax Act also amended Internal Revenue Code Section 174 requiring capitalization of research and experimentation expenditures. The capitalized expenses are amortized over a period of five or fifteen years.

On August 16, 2022, President Biden signed into law the Inflation Reduction Act of 2022, which includes an Alternative Minimum Tax based on the Adjusted Financial Statement Income of Applicable Corporations. Based on our initial evaluation, we do not believe the Inflation Reduction Act will have a material impact on our income tax provision and cash taxes. We continue to monitor the changes in tax laws and regulations to evaluate their potential impact on our business.

Note 16. Net Loss per Share

As the Company had a net loss for the years ended December 31, 2022, 2021 and 2020, all potential weighted average dilutive common shares were determined to be anti-dilutive. The following table sets forth the computation of basic and diluted net loss per share (in thousands, except share and per share data):

	Year Ended December 31,		
	2022	2021	2020
Numerator:			
Net loss	$ (127,393)	$ (125,551)	$ (66,150)
Denominator:			
Weighted-average shares used to compute net loss per common share, basic and diluted	49,042,232	46,322,910	34,396,446
Net loss per share, basic and diluted	$ (2.60)	$ (2.71)	$ (1.92)

The following outstanding shares of potentially dilutive securities have been excluded from diluted net loss per share computations for the periods presented because their inclusion would be anti-dilutive:

	December 31,		
	2022	2021	2020
Options to purchase common stock	6,240,509	5,890,540	4,648,120
Common stock warrants	2,750,000	2,750,000	2,750,000
Restricted stock units	637,436	405,972	244,545
Performance stock units	199,500	105,500	—
ESPP shares	72,598	18,055	28,445
Total	9,900,043	9,170,067	7,671,110

Note 17. Subsequent Event

The Company sold 1,749,199 shares of its common stock under the 2022 ATM Facility pursuant to the Sales Agreement during the period from January 1, 2023 through filing date of this Annual Report on Form 10-K. Net proceeds were $24.3 million, after deducting issuance costs. As of the filing date of this Annual Report on Form 10-K, a total of $275.1 million of common stock remained available for sale under the registration statement on Form S-3 (File No. 333-266595) that was declared effective as of August 16, 2022, $75.1 million of which remained available for sale under the 2022 ATM facility.

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

Management, under the supervision and with the participation of our Chief Executive Officer (Principal Executive Officer) and Chief Financial Officer (Principal Financial Officer), has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act) as of December 31, 2022. Based on the evaluation of our disclosure controls and procedures, our Chief Executive Officer and Chief Financial Officer have concluded that our disclosure controls and procedures as of December 31, 2022 were effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as such term is defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our management, including our Chief Executive Officer and Chief Financial Officer, conducted an evaluation of the effectiveness of our internal control over financial reporting based on the criteria set forth in *Internal Control-Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on its evaluation under the criteria set forth in *Internal Control-Integrated Framework*, our management concluded that our internal control over financial reporting was effective as of December 31, 2022.

Limitations on Effectiveness of Controls and Procedures and Internal Control over Financial Reporting

In designing and evaluating the disclosure controls and procedures and internal control over financial reporting, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures and internal control over financial reporting must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Changes in Internal Control over Financial Reporting

There have been no changes in our internal control over financial reporting that occurred during our most recent fiscal quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers, and Corporate Governance

Except as set forth below, the information required by this item is incorporated herein by reference to information in our definitive proxy statement relating to our 2023 Annual Meeting of Stockholders, which we expect to be filed with the SEC within 120 days of the end of our fiscal year ended December 31, 2022 (the "Proxy Statement"), including under the headings "Election of Directors," "Executive Officers," "Information Regarding Committees of the Board of Directors" and, if applicable, "Delinquent Section 16(a) Reports."

We have adopted a Code of Business Conduct and Ethics that applies to all directors, officers and employees, including our principal executive, principal financial and principal accounting officers, or persons performing similar functions. The Code of Business Conduct and Ethics is posted on our website at www.protagonist-inc.com.

We intend to disclose future amendments to certain provisions of the Code of Business Conduct and Ethics, and waivers of the Code of Business Conduct and Ethics granted to executive officers and directors, on our website listed above within four business days following the date of the amendment or waiver.

Item 11. Executive Compensation

The information required by this item is incorporated herein by reference to information in our Proxy Statement under the headings "Information Regarding Committees of the Board of Directors—Compensation Committee," "—Compensation Committee Interlocks and Insider Participation" and "Executive Compensation."

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

The information required by this item is incorporated herein by reference to information in our Proxy Statement under the heading "Security Ownership of Certain Beneficial Owners and Management" and "Director Compensation—Equity Compensation Plan Information."

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

The information required by this item is incorporated herein by reference to information in our Proxy Statement under the headings "Transactions with Related Persons and Indemnification" and "Information Regarding the Board of Directors and Corporate Governance—Independence of the Board of Directors."

Item 14. Principal Accountant Fees and Services

The information required by this item is incorporated by reference to information in our Proxy Statement under the heading "Ratification of Selection of Independent Registered Public Accounting Firm."

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) The following documents are filed as part of this report:

(1) FINANCIAL STATEMENTS

The financial statements filed as part of this Annual Report on Form 10-K are included in Part II, Item 8 of this Annual Report on Form 10-K.

(2) FINANCIAL STATEMENT SCHEDULES

Financial statement schedules have been omitted in this Annual Report on Form 10-K because they are not applicable, not required under the instructions, or the information requested is set forth in the financial statements or related notes thereto.

(3) EXHIBITS

The exhibits listed in the accompanying Exhibit Index are filed as part of, or incorporated by reference into, this Annual Report on Form 10-K.

(4) EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed Herewith
		Form	SEC File No.	Exhibit	Filing Date	
3.1	Amended and Restated Certificate of Incorporation	8-K	001-37852	3.1	8/16/2016	
3.2	Amended and Restated Bylaws	S-1/A	333-212476	3.2(b)	8/1/2016	
4.1	Specimen stock certificate evidencing the shares of common stock	S-1/A	333-212476	4.1	8/1/2016	
4.3	Description of Protagonist Therapeutics, Inc.'s Securities Registered Pursuant to Section 12 of the Exchange Act					X
10.1+	Protagonist Therapeutics, Inc. 2007 Stock Option and Incentive Plan, as amended and restated, and form of option agreement, exercise notice, joinder, and adoption agreement thereunder.	S-1	333-212476	10.1	7/11/2016	
10.2+	Protagonist Therapeutics, Inc. 2016 Equity Incentive Plan and forms of stock option grant notice, option agreement, notice of exercise, restricted stock unit grant notice and restricted stock unit agreement thereunder.	S-1/A	333-212476	10.2	8/1/2016	
10.3+	Protagonist Therapeutics, Inc. 2016 Employee Stock Purchase Plan.	S-1/A	333-212476	10.3	8/1/2016	
10.4+	Form of Indemnity Agreement for Directors and Officers.	S-1/A	333-212476	10.4	8/1/2016	
10.5+	Protagonist Therapeutics, Inc. Amended and Restated 2018 Inducement Plan, and forms of stock option grant notice, option agreement, restricted stock unit grant notice and restricted stock unit agreement thereunder.	S-8	333-263097	99.3	2/28/2022	
10.6	Lease, dated March 6, 2017, by and between the Registrant and BMR-Pacific Research Center LP.	10-K	001-37852	10.9	3/7/2017	
10.7+	Severance Agreement, dated August 1, 2016, by and between the Registrant and Dinesh Patel.	S-1/A	333-212476	10.9	8/1/2016	
10.8+	Severance Agreement, dated August 1, 2016, by and between the Registrant and David Y. Liu, Ph.D.	S-1/A	333-212476	10.10	8/1/2016	
10.9†	Research and Collaboration Agreement, dated June 16, 2012, by and among the Registrant, Protagonist Pty. Ltd. and Zealand Pharma A/S.	S-1	333-212476	10.17	7/11/2016	

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed Herewith
		Form	SEC File No.	Exhibit	Filing Date	
10.10†	Contract Extension Letter of Agreement, dated June 1, 2013, by and among the Registrant, Protagonist Pty. Ltd. and Zealand Pharma A/S.	S-1	333-212476	10.18	7/11/2016	
10.11†	Agreement on Addition of Additional Collaboration Program, dated September 16, 2013, by and among the Registrant, Protagonist Pty. Ltd. and Zealand Pharma A/S.	S-1	333-212476	10.19	7/11/2016	
10.12†	Protagonist Assumption of Responsibility, dated January 28, 2014, by and between the Registrant and Zealand Pharma A/S.	S-1	333-212476	10.20	7/11/2016	
10.13†	Agreement to Assign Patent Applications, dated February 7, 2014, by and between the Registrant, Protagonist Pty. Ltd. and Zealand Pharma A/S.	S-1	333-212476	10.21	7/11/2016	
10.14†	Abandonment Agreement, dated February 28, 2014, by and among the Registrant, Protagonist Pty. Ltd. and Zealand Pharma A/S.	S-1	333-212476	10.22	7/11/2016	
10.15	Registration Rights Agreement, dated August 8, 2018, by and between the Registrant and certain parties identified on the signature pages thereto	8-K	001-37852	4.3	8/7/2018	
10.16	Securities Purchase Agreement, dated August 6, 2018, by and between the Registrant and certain purchasers identified on the signature pages thereto	S-3	333-227216	10.1	9/7/2018	
10.17	Exchange Agreement, dated December 21, 2018, by and between the Registrant and Biotechnology Value Fund, L.P., Biotechnology Value Fund II, L.P. and Biotechnology Value Trading Fund OS, L.P.	8-K	001-37852	10.1	12/31/2018	
10.18	First Amendment, dated January 31, 2019, to Lease, dated March 6, 2017, by and between Protagonist Therapeutics, Inc., as Tenant, and BMR-Pacific Research Center LP, as Landlord.	10-Q	001-37852	10.3	5/8/2019	
10.19+	Severance Agreement, dated March 14, 2019, by and among Protagonist Therapeutics, Inc. and Suneel Gupta, Ph.D.	10-Q	001-37852	10.4	5/8/2019	

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed Herewith
		Form	SEC File No.	Exhibit	Filing Date	
10.20	Open Market Sale Agreement℠, dated August 5, 2022, by and between Protagonist Therapeutics, Inc. and Jefferies LLC.	S-3	333-266595	1.2	8/5/2022	
10.21	Second Amendment, dated July 2, 2021, to Lease, dated March 6, 2017, by and between Protagonist Therapeutics, Inc., as Tenant, and BMR-Pacific Research Center, LP as Landlord.	10-Q	001-37852	10.3	11/3/2021	
10.22†	Amended and Restated License and Collaboration Agreement, dated July 27, 2021, by and between Protagonist Therapeutics, Inc. and Janssen Biotech, Inc.	10-Q	001-37852	10.1	11/3/2021	
10.23†	Arbitration Resolution Agreement, dated August 4th, 2021, by and among Protagonist Therapeutics, Inc. and Zealand Pharma, A/S.	10-Q	001-37852	10.2	11/3/2021	
10.24+	Employment Offer Letter, by and between Protagonist Therapeutics Inc. and Asif Ali, dated March 25, 2022.	10-Q	001-37852	10.1	5/5/2022	
10.25+	Offer Letter, by and between Protagonist Therapeutics Inc. and Arturo Molina, M.D., Ph.D., dated November 1, 2022.					X
10.26+	Severance Agreement, by and between Protagonist Therapeutics Inc. and Arturo Molina, M.D., Ph.D., dated November 7, 2022.					X
21.1	List of Subsidiaries					X
23.1	Consent of Independent Registered Public Accounting Firm					X
24.1	Power of Attorney (included in signature page of this Form 10-K)					X
31.1	Certification of Chief Executive Officer required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002					X
31.2	Certification of Chief Financial Officer required by Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002					X

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed Herewith
		Form	SEC File No.	Exhibit	Filing Date	
32.1*	Certification of Chief Executive Officer and Chief Financial Officer, as required by Rule 13a-14(b) or Rule 15d-14(b) and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002					X
101.INS	Inline XBRL Instance Document—the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL Document					X
101.SCH	Inline XBRL Taxonomy Extension Schema Document					X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	Inline XBRL Taxonomy Extension Labels Linkbase Document					X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					X
104	Cover Page Interactive Data File—the cover page interactive data file does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document					

+ Indicates management contract or compensatory plan, contract or agreement.

† Certain identified information has been omitted by means of marking such information with asterisks in reliance on Item 601(b)(10)(iv) of Regulation S-K because it is both (i) not material and (ii) the type that the registrant treats as private or confidential.

* This certification attached as Exhibit 32.1 that accompanies this Annual Report on Form 10-K is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Protagonist Therapeutics, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of the Form 10-K, irrespective of any general incorporation language contained in such filing.

Item 16. Form 10-K Summary

None.

SIGNATURES

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

PROTAGONIST THERAPEUTICS, INC.

Date: March 15, 2023

By: /s/ Dinesh V. Patel, Ph.D.
Dinesh V. Patel, Ph.D.
President, Chief Executive Officer and Director
(Principal Executive Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Dinesh V. Patel and Asif Ali, and each of them, his true and lawful attorneys-in-fact, with full power of substitution, for him in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with exhibits thereto and other documents in connection therewith with the Securities and Exchange Commission, hereby ratifying and confirming all that said attorneys-in-fact or any of them or their substitute or substitutes may lawfully do or cause to be done by virtue thereof.

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 in the capacities and on the dates indicated:

Signature	Title	Date
/s/ Dinesh V. Patel, Ph.D. Dinesh V. Patel, Ph.D.	President, Chief Executive Officer and Director *(Principal Executive Officer)*	March 15, 2023
/s/ Asif Ali Asif Ali	Executive Vice President, Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 15, 2023
/s/ Harold E. Selick, Ph.D. Harold E. Selick, Ph.D.	Chairman of the Board of Directors	March 15, 2023
/s/ Bryan Giraudo Bryan Giraudo	Director	March 15, 2023
/s/ Sarah Noonberg, M.D., Ph.D. Sarah Noonberg, M.D., Ph.D.	Director	March 15, 2023
/s/ Sarah O'Dowd Sarah O'Dowd	Director	March 15, 2023
/s/ William D. Waddill William D. Waddill	Director	March 15, 2023
/s/ Lewis T. Williams, M.D., Ph.D. Lewis T. Williams, M.D., Ph.D.	Director	March 15, 2023

7707 Gateway Blvd., Suite 140
Newark, California 94560

NOTICE OF ANNUAL MEETING OF STOCKHOLDERS
To Be Held On May 25, 2023

Dear Stockholder:

You are cordially invited to attend the Annual Meeting of Stockholders (the "Annual Meeting") of Protagonist Therapeutics, Inc., a Delaware corporation (the "Company"). The meeting will be held exclusively online via live audio webcast at www.virtualshareholdermeeting.com/PTGX2023 on Thursday, May 25, 2023 at 10:00 a.m. PDT for the following purposes:

1. To elect the Class I nominee, Dinesh V. Patel, Ph.D., to the Board of Directors to hold office until the 2026 Annual Meeting of Stockholders and until his successor is duly elected and qualified, subject to his earlier resignation or removal.
2. To approve, on an advisory basis, the compensation of the Company's named executive officers.
3. To ratify the selection by the Audit Committee of the Board of Directors of Ernst & Young LLP as the independent registered public accounting firm of the Company for its fiscal year ending December 31, 2023.
4. To conduct any other business properly brought before the meeting.

These items of business are more fully described in the Proxy Statement accompanying this Notice.

The Annual Meeting will be held virtually this year. Online check-in will begin at 9:45 a.m. PDT and you should allow ample time for the check-in procedures. You will not be able to attend the Annual Meeting in person.

The record date for the Annual Meeting is March 31, 2023. Only stockholders of record at the close of business on that date may vote at the meeting or any adjournment or postponement thereof. To participate in the meeting, you must have your 16-digit control number shown on your Notice of Internet Availability of Proxy Materials or on the instructions that accompanied your proxy materials.

Instructions for accessing the virtual Annual Meeting are provided in the Proxy Statement. In the event of a technical malfunction or other situation that the meeting chair determines may affect the ability of the Annual Meeting to satisfy the requirements for a meeting of stockholders to be held by means of remote communication under the Delaware General Corporation Law, or that otherwise makes it advisable to adjourn the Annual Meeting, the meeting chair or secretary will convene the meeting at 11:00 a.m. PDT on the date specified above and at the Company's address specified above solely for the purpose of adjourning the meeting to reconvene at a date, time and physical or virtual location announced by the meeting chair or secretary. Under either of the foregoing circumstances, we will post information regarding the announcement on the Investors page of the Company's website at www.protagonist-inc.com.

By Order of the Board of Directors

/s/ Dinesh V. Patel

Dinesh V. Patel, Ph.D.
President and Chief Executive Officer

Newark, California
April 12, 2023

Whether or not you expect to participate in the virtual Annual Meeting, please vote as promptly as possible in order to ensure your representation at the Annual Meeting. You may vote online or, if you requested printed copies of the proxy materials, by telephone or by using the proxy card or voting instruction form provided with the printed proxy materials.

7707 Gateway Blvd., Suite 140
Newark, California 94560

PROXY STATEMENT
FOR THE 2023 ANNUAL MEETING OF STOCKHOLDERS

To Be Held On Thursday, May 25, 2023

QUESTIONS AND ANSWERS ABOUT THESE PROXY MATERIALS AND VOTING

Why did I receive a notice of internet availability of proxy materials?

Pursuant to rules adopted by the Securities and Exchange Commission (the "SEC"), we have elected to provide access to our proxy materials over the internet. Accordingly, we have sent you a Notice of Internet Availability of Proxy Materials (the "Notice") because the Board of Directors (the "Board") of Protagonist Therapeutics, Inc. (sometimes referred to as the "Company" or "Protagonist") is soliciting your proxy to vote at the 2023 Annual Meeting of Stockholders (the "Annual Meeting"), including at any adjournments or postponements of the meeting. All stockholders will have the ability to access the proxy materials on the website referred to in the Notice or may request a printed set of the proxy materials to be sent to them free of charge. Instructions on how to access the proxy materials over the internet or to request a printed copy may be found in the Notice.

We intend to mail the Notice on or about April 12, 2023 to all stockholders of record entitled to vote at the Annual Meeting.

Will I receive any other proxy materials by mail?

We may send you a proxy card, along with a second Notice, on or after April 25, 2023.

How do I attend and participate in the Annual Meeting?

The Annual Meeting will be held virtually via live webcast at www.virtualshareholdermeeting.com/PTGX2023 on Thursday, May 25, 2023 at 10:00 a.m. PDT. You will not be able to attend the Annual Meeting in person. Stockholders of record as of the close of business on the record date are entitled to participate in and vote at the Annual Meeting. To participate in the Annual Meeting, including to vote and ask questions, stockholders of record should go to the meeting website listed above, enter the 16-digit control number found on your proxy card or Notice, and follow the instructions on the website. Information on how to vote online at the Annual Meeting is discussed below. Online check-in will begin at 9:45 a.m. PDT and stockholders should allow ample time for the check-in procedures. If your shares are held in the name of your broker, bank or other nominee (sometimes referred to as shares held in "street name") and your voting instruction form or Notice indicates that you may vote those shares through www.proxyvote.com, then you may access, participate in and vote at the Annual Meeting with the 16-digit access code indicated on that voting instruction form or Notice. Otherwise, stockholders who hold their shares in street name should contact their bank, broker or other nominee (preferably at least five days before the Annual Meeting) and obtain a "legal proxy" in order to be able to attend, participate in or vote at the Annual Meeting.

Conducting the Annual Meeting virtually increases the opportunity for all stockholders to participate and communicate their views to a much wider audience. The virtual meeting is designed to provide the same rights and advantages of a physical meeting. Stockholders will be able to submit questions online during the meeting, providing our stockholders with the opportunity for meaningful engagement with the Company. Questions must comply with the meeting rules of conduct; the rules of conduct will be posted on the virtual meeting website. We will endeavor to answer as many stockholder-submitted questions as time permits that

comply with the Annual Meeting rules of conduct. We reserve the right to edit profanity or other inappropriate language and to exclude questions regarding topics that are not pertinent to meeting matters or Company business. If we receive substantially similar questions, we may group such questions together and provide a single response to avoid repetition.

Who can vote at the Annual Meeting?

Only stockholders of record at the close of business on March 31, 2023 (the "Record Date") will be entitled to vote at the Annual Meeting. On the Record Date, there were 51,440,503 shares of common stock outstanding and entitled to vote.

Stockholder of record: shares registered in your name

If on the Record Date, your shares were registered directly in your name with Protagonist's transfer agent, American Stock Transfer & Trust Company, LLC, then you are a stockholder of record. As a stockholder of record, you may vote online at the Annual Meeting or vote by proxy. Whether or not you plan to attend the Annual Meeting, we urge you to vote and submit your proxy in advance of the Annual Meeting. For information on how to vote prior to the Annual Meeting, see *"How do I vote?"*.

Beneficial owner: shares registered in the name of a broker or bank

If on the Record Date, your shares were held, not in your name, but rather in an account at a brokerage firm, bank, dealer or other similar organization, then you are the beneficial owner of shares held in "street name" and the Notice is being forwarded to you by that organization. The organization holding your account is considered to be the stockholder of record for purposes of voting at the Annual Meeting. As a beneficial owner, you have the right to direct your broker or other agent regarding how to vote the shares in your account. You are also invited to attend the Annual Meeting virtually via live webcast.

What am I voting on?

There are three matters scheduled for a vote:

- Proposal No. 1 — To elect the Class I nominee to hold office until the 2026 Annual Meeting of Stockholders;
- Proposal No. 2 — To approve, on an advisory basis, the compensation of the Company's named executive officers; and
- Proposal No. 3 — To ratify the selection of Ernst & Young LLP as the Company's independent auditor for 2023.

What if another matter is properly brought before the meeting?

The Board knows of no other matters that will be presented for consideration at the Annual Meeting. If any other matters are properly brought before the meeting, it is the intention of the persons named in the accompanying proxy to vote on those matters in accordance with their best judgment.

How do I vote?

With respect to the election of directors, you may either vote "For" the nominee to the Board or you may "Withhold" your vote for the nominee. For the ratification of the selection of Ernst & Young LLP as the Company's independent auditor for 2023 and for the advisory approval of executive compensation, you may vote "For," "Against" or "Abstain."

The procedures for voting are fairly simple:

Stockholder of record: shares registered in your name

If you are a stockholder of record, you may vote online during the webcast of the Annual Meeting, vote by proxy through the internet or, if you request paper copies of the proxy materials, vote by proxy over the

telephone or mailing a proxy card. Whether or not you plan to attend the meeting online, we urge you to vote by proxy to ensure your vote is counted. You may still attend the meeting and vote online even if you have already voted by proxy.

- To vote online at the Annual Meeting, you must be present via live webcast. To vote live during the meeting, please visit www.virtualshareholdermeeting.com/PTGX2023 and have available the 16-digit control number included in your Notice.
- To vote using the proxy card, simply complete, sign and date the proxy card that may be delivered and return it promptly in the envelope provided. Your signed proxy card must be received by us before the Annual Meeting to be counted.
- To vote over the telephone prior to the Annual Meeting, dial toll-free 1-800-690-6903 and follow the recorded instructions. You will be asked to provide certain information from the Notice. Your telephone vote must be received by 11:59 p.m., Eastern Time on May 24, 2023 to be counted.
- To vote through the internet prior to the Annual Meeting, go to www.proxyvote.com to complete an electronic proxy card. You will be asked to provide certain information from the Notice. Your internet vote must be received by 11:59 p.m., Eastern Time on May 24, 2023 to be counted.

Beneficial owner: shares registered in the name of a broker or bank

If you are a beneficial owner of shares registered in the name of your broker, bank or other agent, you should have received a Notice containing voting instructions from that organization rather than from Protagonist. Simply follow the voting instructions in the Notice to ensure that your vote is counted.

How many votes do I have?

On each matter to be voted upon, you have one vote for each share of common stock you own as of the Record Date.

What happens if I do not vote?

Stockholder of record: shares registered in your name

If you are a stockholder of record and do not vote by completing your proxy card, by telephone, through the internet or online at the Annual Meeting, your shares will not be voted.

Beneficial owner: shares registered in the name of a broker or bank

If you are a beneficial owner of shares registered in "street name" and you do not provide the broker or other nominee that holds your shares with voting instructions, whether your broker or nominee will still be able to vote your shares depends on whether the particular proposal is a "routine" matter. Brokers and other nominees can use their discretion to vote "uninstructed" shares with respect to matters that are considered to be "routine," but not with respect to "non-routine" matters. Whether a proposal is considered routine or non-routine is subject to stock exchange rules and final determination by the stock exchange. Even with respect to routine matters, some brokers are choosing not to exercise discretionary voting authority. As a result, we urge you to direct your broker, bank or other nominee how to vote your shares on all proposals to ensure that your vote is counted.

What if I am a stockholder of record and return a proxy card or otherwise vote but do not make specific choices?

If you are a stockholder of record and return a signed and dated proxy card or otherwise vote without marking voting selections, your shares will be voted, as applicable:

- "For" the election of the Class I nominee for director;
- "For" the advisory approval of the compensation of the Company's named executive officers; and
- "For" the ratification of Ernst & Young LLP as the Company's independent auditor for 2023.

If any other matter is properly presented at the Annual Meeting, your proxyholder (one of the individuals named on your proxy card) will vote your shares using his or her best judgment.

Who is paying for this proxy solicitation?

We will pay for the entire cost of soliciting proxies. In addition to these proxy materials, our directors and employees may also solicit proxies in person, by telephone or by other means of communication. Directors and employees will not be paid any additional compensation for soliciting proxies. We may also reimburse brokerage firms, banks and other agents for the cost of forwarding proxy materials to beneficial owners.

What does it mean if I receive more than one Notice?

If you receive more than one Notice, your shares may be registered in more than one name or in different accounts. Please cast your vote with respect to each set of proxy materials that you receive to ensure that all of your shares are voted.

Can I change my vote after submitting my proxy?

Stockholder of record: shares registered in your name

Yes. You can revoke your proxy at any time before the final vote at the meeting. If you are the record holder of your shares, you may revoke your proxy in any one of the following ways:

- You may submit another properly completed proxy card with a later date.
- You may grant a subsequent proxy by telephone or through the internet.
- You may send a timely written notice that you are revoking your proxy to Protagonist's Corporate Secretary at 7707 Gateway Blvd., Suite 140, Newark, California 94560.
- You may attend the Annual Meeting and vote online by visiting www.virtualshareholdermeeting.com/PTGX2023. To attend the meeting, you will need the 16-digit control number included in your Notice or on the instructions that accompanied your proxy materials. Simply attending the meeting will not, by itself, revoke your proxy.

Your last submitted vote is the one that is counted.

Beneficial owner: shares registered in the name of a broker or bank

If your shares are held by your broker, bank or other nominee, you should follow the instructions provided by your broker, bank or other nominee.

When are stockholder proposals and director nominations due for next year's Annual Meeting?

Pursuant to Rule 14a-8 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), to be considered for inclusion in next year's proxy materials, your proposal must be submitted in writing to our Corporate Secretary at the address set forth on the first page of this Proxy Statement. Such proposals must be received by us as of the close of business (6:00 p.m. PDT) on December 14, 2023 and must comply with Rule 14a-8 of the Exchange Act. The submission of a stockholder proposal does not guarantee that it will be included in the proxy statement.

As set forth in our Amended and Restated Bylaws, if you intend to make a nomination for director election or present a proposal for other business (other than pursuant to Rule 14a-8 of the Exchange Act) at the 2024 Annual Meeting of Stockholders, you must provide specified information in writing to our Corporate Secretary at the address above no earlier than January 26, 2024 and no later than the close of business (6:00 p.m. PDT) on February 25, 2024; provided, however, that if our 2024 Annual Meeting of Stockholders is held before April 25, 2024 or after June 24, 2024, notice by the stockholder to be timely must be received no earlier than the close of business on the 120th day prior to such annual meeting and not later than the close of business on the later of the 90th day prior to such annual meeting or the 10th day following the day on which public announcement of the date of such meeting is first made. Any such director nomination or stockholder

proposal must be a proper matter for stockholder action and must comply with the terms and conditions set forth in our Amended and Restated Bylaws. If you fail to meet these deadlines or fail to satisfy the requirements of Rule 14a-4 of the Exchange Act, we may exercise discretionary voting authority under proxies we solicit to vote on any such proposal as we determine appropriate. In addition to satisfying the deadlines in the advance notice provisions of our Amended and Restated Bylaws, if you intend to solicit proxies in support of nominees submitted under these advance notice provisions for the 2024 Annual Meeting of Stockholders, you must provide the notice required under Rule 14a-19 of the Exchange Act to our Corporate Secretary in writing not later than the close of business (6:00 p.m. PDT) on March 26, 2024. You are also advised to review our Amended and Restated Bylaws, which contain additional requirements about advance notice of stockholder proposals and director nominations. We reserve the right to reject, rule out of order or take other appropriate action with respect to any nomination or proposal that does not comply with these and other applicable requirements.

Who will count the votes?

Votes will be counted by Broadridge Financial Solutions, the inspector of election appointed for the meeting

What are "broker non-votes"?

As discussed above, when a beneficial owner of shares held in "street name" does not give instructions to the broker or other nominee holding the shares as to how to vote, the broker or other nominee cannot vote those shares on matters deemed to be "non-routine" and may choose not to vote those shares on matters deemed to be "routine." These unvoted shares are considered "broker non-votes."

How many votes are needed to approve each proposal?

The following table summarizes the minimum vote needed to approve each proposal and the effect of abstentions and broker non-votes.

Proposal Number	Proposal Description	Vote Required for Approval	Effect of Abstentions	Effect of Broker Non-Votes
1	Election of director nominee	Nominee receiving the most "For" votes; withheld votes will have no effect.	Under plurality voting, there are no abstentions.	None
2	Advisory approval of the compensation of our named executive officers	"For" votes from the holders of a majority of shares present online during the virtual meeting or represented by proxy and entitled to vote on the matter.	Against	None
3	Ratification of the selection of Ernst & Young LLP as the Company's independent auditor for fiscal year ending December 31, 2023	"For" votes from the holders of a majority of shares present online during the virtual meeting or represented by proxy and entitled to vote on the matter.	Against	None

What is the quorum requirement?

A quorum of stockholders is necessary to transact business at the meeting. A quorum will be present if stockholders holding a majority of the outstanding shares entitled to vote are present at the meeting online or represented by proxy.

Your shares will be counted towards the quorum only if you submit a valid proxy (or one is submitted on your behalf by your broker, bank or other nominee) or if you vote online at the meeting. Abstentions and broker non-votes will be counted towards the quorum requirement. If there is no quorum, the meeting chair or the holders of a majority of shares present at the meeting online or represented by proxy may adjourn the meeting to another time or date.

How can I find out the results of the voting at the Annual Meeting?

Preliminary voting results will be announced at the Annual Meeting. In addition, final voting results will be published in a Current Report on Form 8-K that we expect to file within four business days after the Annual Meeting.

Important Notice Regarding the Availability of Proxy Materials for the 2023 Annual Meeting of Stockholders to Be Held on May 25, 2023. The Proxy Statement and Annual Report on Form 10-K for the year ended December 31, 2022 are available at www.proxyvote.com.

LEGAL MATTERS

Forward-Looking Statements. The Proxy Statement may contain "forward-looking statements" within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995, which statements are subject to substantial risks and uncertainties and are based on estimates and assumptions. All statements other than statements of historical fact included in the Proxy Statement are forward-looking statements, including statements about the Company's Board of Directors, corporate governance practices, executive compensation program, equity compensation utilization and environmental, social and governance ("ESG") initiatives. In some cases, you can identify forward-looking statements by terms such as "may," "might," "will," "objective," "intend," "should," "could," "can," "would," "expect," "believe," "design," "estimate," "predict," "potential," "plan" or the negative of these terms, and similar expressions intended to identify forward-looking statements. These statements involve known and unknown risks, uncertainties and other factors that could cause our actual results to differ materially from the forward-looking statements expressed or implied in the Proxy Statement. Such risks, uncertainties and other factors include those identified in the Company's Annual Report on Form 10-K for the year ended December 31, 2022 filed with the SEC and other subsequent documents we file with the SEC. The Company expressly disclaims any obligation to update or alter any statements whether as a result of new information, future events or otherwise, except as required by law.

Website References. Website references throughout this document are inactive textual references and provided for convenience only, and the content on the referenced websites is not incorporated herein by reference and does not constitute a part of the Proxy Statement.

Use of Trademarks. Protagonist Therapeutics is the trademark of Protagonist Therapeutics, Inc. Other names and brands may be claimed as the property of others.

PROPOSAL 1

ELECTION OF DIRECTOR NOMINEE

Protagonist's Board is divided into three classes. Each class consists of approximately one-third of the total number of directors, and each class is elected for a three-year term. Vacancies on the Board may be filled only by persons elected by a majority of the remaining directors. A director elected by the Board to fill a vacancy in a class, including vacancies created by an increase in the number of directors, shall serve for the remainder of the full term of that class and until the director's successor is duly elected and qualified.

The Board currently consists of seven members. The terms of office of our two Class I directors expire at this Annual Meeting. Sarah Noonberg, M.D., Ph.D., one of our Class I directors, is not standing for re-election at the Annual Meeting and will cease to be a director upon the expiration of her term. In accordance with our Amended and Restated Bylaws, the Board has determined to decrease its size to six directors effective as of such time. The Nominating and Corporate Governance Committee has recommended Dr. Patel for election to the Board at this Annual Meeting. Dr. Patel is currently a director of the Company and was previously elected by stockholders at the 2020 Annual Meeting of Stockholders. If elected at the Annual Meeting, Dr. Patel would serve until the 2026 Annual Meeting of Stockholders and until his successor has been duly elected and qualified, or, if sooner, until his death, resignation or removal. It is the Company's policy to encourage directors and director nominees to attend Annual Meetings of Stockholders. Five of our directors then serving on the Board attended the 2022 Annual Meeting of Stockholders.

Directors are elected by a plurality of the votes cast. Accordingly, the nominee receiving the highest number of affirmative votes will be elected. Shares represented by executed proxies will be voted, if authority to do so is not withheld, for the election of Dr. Patel. If he becomes unavailable for election or unable to serve, shares that would have been voted for him will instead be voted for the election of a substitute nominee proposed by the Board or the Board may decrease the size of the Board. Dr. Patel has agreed to serve if elected. The Company's management has no reason to believe that he will be unable to serve.

The brief biographies below include information, as of the date of this Proxy Statement, regarding the specific and particular experiences, qualifications, attributes or skills of the director nominee and each director continuing in office that caused the Nominating and Corporate Governance Committee and the Board to determine that the applicable nominee or director should serve as a member of the Board.

CLASS I DIRECTOR NOMINEE FOR ELECTION FOR A THREE-YEAR TERM EXPIRING AT THE 2026 ANNUAL MEETING

Dinesh V. Patel, Ph.D.

Dr. Patel, 66, has served as a member of the Board and as the Company's President and Chief Executive Officer since December 2008. Dr. Patel has more than 37 years of executive, entrepreneurial and scientific experience spanning the pharmaceutical, biotechnology and biopharmaceutical industries. Prior to joining Protagonist, he served from 2006 to 2008 as the President and Chief Executive Officer of Arête Therapeutics, a privately held company focused on the development of novel drugs for metabolic syndrome. Prior to that, Dr. Patel was President, Chief Executive Officer and co-founder of Miikana Therapeutics, an oncology-based company, from 2003 until it was acquired by Entremed (later renamed CASI Pharmaceuticals) in 2005. Prior to Miikana, he held positions of increasing responsibility at Versicor, a biotechnology company, (later renamed Vicuron and which was acquired by Pfizer in 2005), from 1996 to 2003, most recently as Senior Vice President of Drug Discovery and Licensing. Prior to Vicuron, Dr. Patel was a director of chemistry at the combinatorial chemistry company Affymax (OTCMKTS: AFFY), from 1993 to 1996. He was also a medicinal chemist at Bristol Myers Squibb (NYSE: BMY) from 1985 to 1993. Dr. Patel received a Ph.D. in Chemistry from Rutgers University, New Jersey and a B.S. in Industrial Chemistry from S. P. University, Vallabh Vidyanagar, India. The Company believes that because of his expertise, extensive knowledge of the Company and experience as an executive officer of biotechnology companies, Dr. Patel is able to make valuable contributions to the Board.

THE BOARD OF DIRECTORS RECOMMENDS A VOTE "FOR" THE NAMED NOMINEE.

In addition to the Class I director nominee, Protagonist has five other directors who will continue in office after the Annual Meeting, with terms expiring in 2024 and 2025.

CLASS II DIRECTORS CONTINUING IN OFFICE UNTIL THE 2024 ANNUAL MEETING

Sarah A. O'Dowd

Ms. O'Dowd, 73, has served as a member of the Board since August 2020. Ms. O'Dowd is a member of the board of directors of Ichor Holdings, Ltd., a leader in the design, engineering and manufacturing of critical fluid delivery subsystems and components for semiconductor capital equipment, and is a director of the Independent Institute, a non-profit, non-partisan, public policy research and communications organization. Until her retirement in March 2020, she was Senior Vice President and Chief Legal Officer at Lam Research Corporation (Nasdaq: LRCX), an S&P 500 technology company. For 11 years at Lam, she served as Chief Legal Officer and Secretary. From 2009 to 2012 she also served as Group Vice President of Human Resources at Lam. From February 2007 to September 2008, she served as Vice President of FibroGen, Inc. (Nasdaq: FGEN), a biopharmaceutical company. Ms. O'Dowd received a J.D. from Stanford Law School, an M.A. in Communications from Stanford University and an A.B. in Mathematics from Immaculata College. The Company believes that because of her executive business experience as well as her experience in the biotechnology field and at public companies, Ms. O'Dowd is well positioned to make valuable contributions and provide valuable guidance to the Board.

William D. Waddill

Mr. Waddill, 66, has served as a member of the Board since July 2016. From April 2014 to December 2016, Mr. Waddill served as Senior Vice President and Chief Financial Officer, Treasurer and Secretary of Calithera Biosciences, Inc. (Nasdaq: CALA), a biotechnology company. From October 2007 to March 2014, he served as Senior Vice President and Chief Financial Officer of OncoMed Pharmaceuticals, Inc., a biopharmaceutical company. From October 2006 to September 2007, Mr. Waddill served as the Senior Vice President, Chief Financial Officer of Ilypsa, Inc., a biotechnology company that was acquired in 2007 by Amgen, Inc. From February 2000 to September 2006, he served as a Principal at Square One Finance, a financial consulting business. He has served as a director of Arrowhead Pharmaceuticals, Inc. (Nasdaq: ARWR), a biopharmaceutical company, since January 2018 and Annexon, Inc. (Nasdaq: ANNX), a biopharmaceutical company, since August 2021. Mr. Waddill received a B.S. in Accounting from the University of Illinois, Chicago, and a certification as a public accountant, which is currently inactive, after working at PricewaterhouseCoopers LLP and Deloitte LLP. The Company believes that Mr. Waddill is qualified to serve on the Board because of his financial expertise and extensive experience in the biotechnology field.

Lewis T. "Rusty" Williams, M.D., Ph.D.

Dr. Williams, 73, has served as a member of the Board since June 2017. He has served as Chairman and Chief Executive Officer of Walking Fish Therapeutics, a biotechnology start-up company, since February 2019. Dr. Williams has also served as a venture partner of Quan Capital, LLP, a healthcare-focused venture capital firm, since October 2018. Dr. Williams founded and served as a director of Five Prime Therapeutics, Inc., a former public biotechnology company acquired by Amgen, Inc. from January 2002 until January 2020, and served as its President and Chief Executive Officer from April 2011 to December 2017. Previously, Dr. Williams spent seven years at Chiron Corporation, a biopharmaceutical company now known as Novartis Vaccines and Diagnostics, Inc., where he served most recently as its Chief Scientific Officer. He also served on Chiron's board of directors from 1999 to 2001. Prior to joining Chiron, Dr. Williams was a professor of medicine at the University of California, San Francisco, and served as Director of the University's Cardiovascular Research Institution and Daiichi Research Center. Dr. Williams also has served on the faculties of Harvard Medical School and Massachusetts General Hospital and co-founded COR Therapeutics, Inc., a biotechnology company focused on cardiovascular disease. He is a member of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences. Dr. Williams was previously a member

of the board of directors of Neoleukin Therapeutics, Inc. (Nasdaq: NLTX), COR Therapeutics, Inc., and Beckman Coulter, Inc., each of which was a public company during his service as a director. Dr. Williams received a B.S. from Rice University and an M.D. and a Ph.D. from Duke University. The Company believes that Dr. Williams' extensive experience in drug discovery and development, his executive experience with several pharmaceutical companies and his service as a director of other publicly traded healthcare companies have provided him the qualifications, skills and financial expertise to serve on the Board.

CLASS III DIRECTORS CONTINUING IN OFFICE UNTIL THE 2025 ANNUAL MEETING

Harold E. Selick, Ph.D.

Dr. Selick, 68, has served as a member of the Board since February 2009. Dr. Selick is currently Chief Executive Officer and board member of Hinge Bio, Inc., a private biotechnology company focused on developing therapeutics for patients living with cancer. He previously served as Vice Chancellor of Business Development, Innovation and Partnerships at the University of California, San Francisco, from April 2017 to December 2022. Dr. Selick was a Venture Partner at Mission Bay Capital, a venture capital firm, from 2018 until his resignation at the end of 2022. Previously, he was the Chief Executive Officer of Threshold Pharmaceuticals, Inc., a biotechnology company, from June 2002 until the company's merger with Molecular Templates Inc. in April 2017. From June 2002 until July 2007, Dr. Selick was also a Venture Partner of Sofinnova Ventures, Inc., a venture capital firm. From January 1999 to April 2002, he was Chief Executive Officer of Camitro Corporation, a biotechnology company, which was acquired two years after its founding. From 1992 to 1999, he was at Affymax Research Institute, the drug discovery technology development center for Glaxo Wellcome plc, most recently as Vice President of Research. Prior to working at Affymax he held scientific positions at Protein Design Labs, Inc. and Anergen, Inc. Dr. Selick serves as Chairman of the board of directors of Molecular Templates, Inc. (Nasdaq: MTEM), a biopharmaceutical company. Dr. Selick previously served as Lead Director and then Chairman of PDL BioPharma, Inc., a biopharmaceutical company, from 2009 to December 2019, and served as Chairman of the board of directors of Threshold Pharmaceuticals, Inc. until it merged with Molecular Templates Inc. in April 2017. Dr. Selick received a B.A. in Biophysics and a Ph.D. in Biology from the University of Pennsylvania and was a Damon Runyon-Walter Winchell Cancer Fund Fellow and an American Cancer Society Senior Fellow at the University of California, San Francisco. The Company believes that because of his broad experience in building and running both private and public companies and serving on the boards of directors of a variety of biotechnology companies, Dr. Selick is well positioned to provide guidance and insight to the Board and management team.

Bryan Giraudo

Mr. Giraudo, 47, has served as a member of the Board since May 2018. Mr. Giraudo has also served as Chief Financial Officer of Gossamer Bio, Inc. (Nasdaq: GOSS), a biotechnology company, since May 2018 and Chief Operating Officer since September 2021. He has completed nearly $1.0 billion in financings for Gossamer Bio since inception, from Series B financing through its initial public offering and additional debt and equity financings. Prior to joining Gossamer Bio, Mr. Giraudo was a Senior Managing Director at Leerink Partners (now known as SVB Leerink) from 2009 to April 2018, where he was responsible for their western North America and Asia Pacific biotechnology and medical technology banking practice. Before joining Leerink, he was a Managing Director with Merrill Lynch and Co.'s Global Healthcare Investment Banking Group. Mr. Giraudo joined Merrill Lynch in 1997. As a banker, he completed over 200 corporate finance, corporate partnership and strategic advisory transactions. Mr. Giraudo has been a member of the board of directors of Onxeo SA (EPA: ALONX), a biotechnology company, since November 2021. He received a B.A. from Georgetown University. The Company believes Mr. Giraudo is qualified to serve on the Board because of his extensive experience in the investment banking field, financial expertise and experience in the biotechnology field.

INFORMATION REGARDING THE BOARD OF DIRECTORS AND CORPORATE GOVERNANCE

INDEPENDENCE OF THE BOARD OF DIRECTORS

As required under the Nasdaq Stock Market ("Nasdaq") listing standards, a majority of the members of a listed company's board must qualify as "independent," as affirmatively determined by the board. The Board

consults with the Company's counsel to ensure that the Board's determinations are consistent with relevant securities and other laws and regulations regarding the definition of "independent," including those set forth under the listing standards of Nasdaq, as in effect from time to time.

Consistent with these considerations, after a review of all relevant identified transactions or relationships between each director, or any of his or her family members, and the Company, its senior management and its independent auditor, the Board has affirmatively determined that the following five directors are independent directors within the meaning of the applicable Nasdaq listing standards: Mr. Giraudo, Dr. Selick, Ms. O'Dowd, Mr. Waddill and Dr. Williams. Dr. Noonberg, who is not standing for re-election at the Annual Meeting, is also deemed to be independent. In making this determination, the Board found that none of these directors had material or other disqualifying relationships with the Company. Dr. Patel is not considered independent because he is an executive officer of the Company.

In making the above independence determinations, the Board takes into account certain relationships and transactions that occur in the ordinary course of business between the Company and entities with which some of its directors are or have been affiliated.

BOARD LEADERSHIP STRUCTURE

The Board has an independent Chairperson of the Board ("Chairperson"), Dr. Selick, who has authority, among other things, to call and preside over meetings of the Board, including meetings of the independent directors, to set meeting agendas and to determine materials to be distributed to the Board. Accordingly, the Chairperson has substantial ability to shape the work of the Board. The Company believes that separation of the positions of Chairperson and Chief Executive Officer reinforces the independence of the Board in its oversight of the business and affairs of the Company. In addition, the Company believes that having an independent Chairperson creates an environment that is more conducive to objective evaluation and oversight of management's performance, increases management accountability and improves the ability of the Board to monitor whether management's actions are in the best interests of the Company and its stockholders. As a result, the Company believes that having an independent Chairperson can enhance the effectiveness of the Board as a whole.

ROLE OF THE BOARD IN RISK OVERSIGHT

The Board has responsibility for the oversight of the Company's risk management processes and, either as a whole or through its committees, regularly discusses with management the Company's major risk exposures, their potential impact on the Company's business and the steps taken to manage them. The risk oversight process includes receiving regular reports from Board committees and members of senior management to enable the Board to understand the Company's risk identification, risk management and risk mitigation strategies with respect to areas of potential material risk, including operations, finance, legal, regulatory, strategic and reputational risk. The Audit Committee reviews information regarding liquidity and operations and oversees the Company's management of financial risks. Periodically, the Audit Committee reviews the Company's policies with respect to risk assessment, risk management, loss prevention and regulatory compliance. Oversight by the Audit Committee includes direct communication with the Company's external auditor, and discussions with management regarding significant risk exposures and the actions management has taken to limit, monitor or control such exposures. The Compensation Committee is responsible for assessing whether any of the Company's compensation policies or programs has the potential to encourage excessive risk taking. The Nominating and Corporate Governance Committee manages risks associated with the independence of the Board, corporate disclosure practices and potential conflicts of interest. While each committee is responsible for evaluating certain risks and overseeing the management of such risks, the entire Board is regularly informed through committee reports about such risks. Matters of significant strategic risk are considered by the Board as a whole.

MEETINGS OF THE BOARD OF DIRECTORS

The Board met six times during the last fiscal year. Each Board member attended 75% or more of the aggregate number of meetings of the Board and of the committees on which he or she served during the portion of the last fiscal year for which he or she was a director or committee member.

The independent directors have the opportunity to meet in executive sessions without management present at every regular Board meeting and at such other times as may be determined by the Chairperson. The purpose of these executive sessions is to encourage and enhance communication among independent directors. In fiscal 2022, the Company's independent directors met four times in executive sessions at which only independent directors were present. Dr. Selick, the Chairperson, presides over the executive sessions.

INFORMATION REGARDING COMMITTEES OF THE BOARD OF DIRECTORS

The Board has three committees: an Audit Committee, a Compensation Committee and a Nominating and Corporate Governance Committee. The following table provides current membership and meeting information for fiscal 2022 for each of the Board committees:

Name	Audit	Compensation	Nominating and Corporate Governance
Bryan Giraudo	X	—	X*
Sarah Noonberg, M.D., Ph.D.[(1)]	X	—	—
Sarah A. O'Dowd	—	—	X
Dinesh V. Patel, Ph.D.	—	—	—
Harold E. Selick, Ph.D.	—	X*	X
William D. Waddill	X*	X	—
Lewis T. Williams, M.D., Ph.D.	—	X	—
Total meetings in fiscal 2022	6	3	4

* Committee Chairperson

(1) Following the Annual Meeting, Dr. Noonberg will no longer serve as a director and will cease to be a member of the Audit Committee.

Each of the committees has authority to engage legal counsel or other experts or consultants, as it deems appropriate to carry out its responsibilities. The Board has determined that each member of each committee meets the applicable Nasdaq and SEC rules and regulations regarding "independence" for service on such committee (and, in the case of Compensation Committee members, qualifies as a "non-employee director") and each member is free of any relationship that would impair his or her individual exercise of independent judgment with regard to the Company. The Board has adopted written charters for each committee that are available to stockholders in the "Corporate Governance" section of the Company's website at www.protagonist-inc.com. Below is a description of each committee of the Board.

Audit Committee

The Audit Committee oversees the Company's corporate accounting and financial reporting processes and audits of its financial statements. For this purpose, the Audit Committee performs several functions. The Audit Committee evaluates the performance of and assesses the qualifications of the independent auditor; determines and approves the engagement of the independent auditor; determines whether to retain or terminate the existing independent auditor or to appoint and engage a new independent auditor; reviews and approves the retention of the independent auditor to perform any proposed permissible non-audit services; monitors the rotation of partners of the independent auditor on the Company's audit engagement team as required by law; reviews and approves or rejects transactions between the Company and any related persons; confers with management and the independent auditor regarding the effectiveness of internal control over financial reporting; establishes procedures, as required under applicable law, for the receipt, retention and treatment of complaints received by the Company regarding accounting, internal accounting controls or auditing matters and the confidential and anonymous submission by employees of concerns regarding questionable accounting or auditing matters; and meets to review the Company's annual audited financial statements and quarterly financial statements with management and the independent auditor, including a review of the Company's disclosures under "Management's Discussion and Analysis of Financial Condition and Results of Operations."

The Board has determined that Mr. Waddill qualifies as an "audit committee financial expert," as defined in applicable SEC rules. The Board made a qualitative assessment of Mr. Waddill's level of knowledge and experience based on a number of factors, including his formal education and experience as a chief financial officer for public companies. The Board has also determined that all members of the Audit Committee are "financially literate" under Nasdaq listing rules.

Report of the Audit Committee of the Board of Directors

The Audit Committee has reviewed and discussed the audited financial statements for the fiscal year ended December 31, 2022 with management of the Company and with Ernst & Young LLP, the Company's independent registered public accounting firm. The Audit Committee has discussed with Ernst & Young LLP the matters required to be discussed by the applicable requirements of the Public Company Accounting Oversight Board ("PCAOB") and the SEC. The Audit Committee has also received the written disclosures and the letter from Ernst & Young LLP required by applicable requirements of the PCAOB regarding the independent accountant's communications with the Audit Committee concerning independence and has discussed with Ernst & Young LLP the accounting firm's independence. Based on the foregoing, the Audit Committee has recommended to the Board that the audited financial statements be included in the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2022.

Mr. William D. Waddill
Mr. Bryan Giraudo
Dr. Sarah Noonberg

Compensation Committee

The Compensation Committee acts on behalf of the Board to review, adopt and oversee the Company's compensation strategy, policies, plans and programs, including:

- determining the compensation and other terms of employment of the Chief Executive Officer and the other executive officers and reviewing and approving corporate performance goals and objectives relevant to such compensation;
- reviewing and recommending to the full Board the compensation of the Company's directors;
- evaluating and administering the equity incentive plans, compensation plans and similar programs advisable for us, as well as reviewing and recommending to the Board the adoption, modification or termination of the Company's plans and programs;
- establishing policies with respect to equity compensation arrangements; and
- conducting an annual assessment of the performance of the Compensation Committee and its members, and the adequacy of its charter.

Compensation Committee Processes and Procedures

Typically, the Compensation Committee meets as often as its members deem necessary or appropriate. The agenda for each meeting is usually developed by the Chairperson of the Compensation Committee, in consultation with the Company's Chief Executive Officer. The Compensation Committee meets regularly in executive session. However, from time to time, various members of management and other employees as well as outside advisors or consultants may be invited by the Compensation Committee to make presentations, to provide financial or other background information or advice or to otherwise participate in Compensation Committee meetings. The Chief Executive Officer may not participate in, or be present during, any deliberations or determinations of the Compensation Committee regarding his compensation or individual performance objectives. The charter of the Compensation Committee grants the Compensation Committee full access to all books, records, facilities and personnel of the Company. In addition, under the charter, the Compensation Committee has the authority to obtain, at the expense of the Company, advice and assistance from compensation consultants and internal and external legal, accounting or other advisors and other external resources that the Compensation Committee considers necessary or appropriate in the performance of its duties. The Compensation Committee has direct responsibility for the oversight of the work of any consultants or advisers engaged for the purpose of advising the committee. In particular, the Compensation

Committee has the sole authority to retain, in its sole discretion, compensation consultants to assist in its evaluation of executive and director compensation, including the authority to approve the consultant's reasonable fees and other retention terms. Under the charter, the Compensation Committee may select, or receive advice from, a compensation consultant, legal counsel or other adviser to the compensation committee, other than in-house legal counsel and certain other types of advisers, only after taking into consideration six factors, prescribed by the SEC and Nasdaq, that bear upon the adviser's independence; however, there is no requirement that any adviser be independent.

During the past fiscal year, after taking into consideration the six factors prescribed by the SEC and Nasdaq described above, the Compensation Committee engaged Radford, an Aon Hewitt Company, as compensation consultant. Radford was selected because it is a well-known and respected national compensation consulting firm that commonly provides information, recommendations and other executive compensation advice to compensation committees and management. The Compensation Committee has determined that (1) Radford satisfies applicable independence criteria and (2) Radford's work does not raise any conflicts of interest, in each case under applicable Nasdaq and SEC rules and regulations. The Compensation Committee requested that Radford:

- evaluate the efficacy of the Company's existing compensation strategy and practices in supporting and reinforcing the Company's long-term strategic goals; and
- assist in refining the Company's compensation strategy and in developing and implementing an executive compensation program to execute that strategy.

As part of its engagement, Radford was requested by the Compensation Committee to develop a comparative group of companies and to perform analyses of competitive performance and compensation levels for that group; as well as conduct market research and analysis on annual and long-term incentive programs, salaries, and equity plans; assist in developing target grant levels, target bonus levels, and annual salaries for executive officers and other employees; provide the committee with advice and ongoing recommendations regarding material executive compensation decisions; and review the director compensation program. Radford ultimately developed recommendations that were presented to the Compensation Committee for its consideration. Following an active dialogue with Radford and resulting modifications, the Compensation Committee approved the modified Radford recommendations.

On May 25, 2017, the Compensation Committee amended its New Hire and Merit Equity Grant Delegation Policy pursuant to which delegated authority was granted to Dr. Patel, as the sole member of the Equity Award Committee of the Board, the full authority of the Board, to grant equity-based awards, within Board-approved guidelines, under the Company's 2016 Equity Incentive Plan (the "2016 Plan"). The purpose of this delegation of authority is to enhance the flexibility of option administration within the Company and to facilitate the timely grants of equity-based awards to service providers of the Company.

During fiscal 2022, Dr. Patel exercised his authority to grant options to purchase an aggregate of 1,057,125 shares to employees.

The Compensation Committee and the Board retain concurrent authority to make equity-based awards to employees and consultants who are eligible recipients under this policy pursuant to the 2016 Plan. The Compensation Committee receives periodic reports of grants made pursuant to this delegated authority.

Historically, the Compensation Committee has made most of the significant adjustments to annual compensation, determined bonus and equity-based awards and established new performance objectives at one or more meetings held during the first quarter of the year. However, the Compensation Committee also considers matters related to individual compensation, such as compensation for new executive hires, as well as high-level strategic issues, such as the efficacy of the Company's compensation strategy, potential modifications to that strategy and new trends, plans or approaches to compensation, at various meetings throughout the year. Generally, the Compensation Committee's process comprises two related elements: the determination of compensation levels and the establishment of performance objectives for the current year. For executives other than the Chief Executive Officer, the Compensation Committee solicits and considers evaluations and recommendations submitted to the committee by the Chief Executive Officer. In the case of the Chief Executive Officer, the evaluation of his performance is conducted by the Compensation Committee, which determines any adjustments to his compensation as well as awards to be granted. For all executives and

directors as part of its deliberations, the Compensation Committee may review and consider, as appropriate, materials such as financial reports and projections, operational data, tax and accounting information, tally sheets that set forth the total compensation that may become payable to executives in various hypothetical scenarios, executive and director stock ownership information, Company stock performance data, analyses of historical executive compensation levels and current Company-wide compensation levels and recommendations of the Compensation Committee's compensation consultant, including analyses of executive and director compensation paid at other companies identified by the consultant.

Compensation Committee Interlocks and Insider Participation

None of the members of the Compensation Committee is currently or has been at any time one of the Company's officers or employees. None of the Company's executive officers currently serves, or has served during the last year, as a member of the board or compensation committee of any entity that has one or more executive officers serving as a member of the Board or Compensation Committee.

Nominating and Corporate Governance Committee

The Nominating and Corporate Governance Committee is responsible for identifying, reviewing and evaluating candidates to serve as directors of the Company (consistent with criteria approved by the Board); recommending to the Board for selection candidates for election to the Board; making recommendations to the Board regarding the membership of the committees of the Board; assessing the performance of the Board; and developing a set of corporate governance principles for the Company.

The Nominating and Corporate Governance Committee believes that candidates for director should have certain minimum qualifications, including the ability to read and understand basic financial statements and having the highest personal integrity and ethics. The Nominating and Corporate Governance Committee also considers such factors as possessing relevant expertise upon which to be able to offer advice and guidance to management, having sufficient time to devote to the affairs of the Company, demonstrated excellence in his or her field, having the ability to exercise sound business judgment and having the commitment to rigorously represent the long-term interests of the Company's stockholders. However, the Nominating and Corporate Governance Committee retains the right to modify these qualifications from time to time. Candidates for director nominees are reviewed in the context of the current composition of the Board, the operating requirements of the Company and the long-term interests of stockholders. In conducting this assessment, the Nominating and Corporate Governance Committee typically considers diversity (as discussed below), age, skills and such other factors as it deems appropriate, given the current needs of the Board and the Company, to maintain a balance of knowledge, experience and capability.

The Nominating and Corporate Governance Committee appreciates the value of thoughtful Board refreshment, and regularly identifies and considers qualities, skills and other director attributes that would enhance the composition of the Board. In the case of incumbent directors whose terms of office are set to expire, the Nominating and Corporate Governance Committee reviews these directors' overall service to the Company during their terms, including the number of meetings attended, level of participation, quality of performance and any other relationships and transactions that might impair the directors' independence. The committee also takes into account the results of the Board's self-evaluation. In the case of new director candidates, the Nominating and Corporate Governance Committee also determines whether the nominee is independent based upon applicable Nasdaq listing standards, applicable SEC rules and regulations and the advice of counsel, if necessary. The Nominating and Corporate Governance Committee then uses its network of contacts to compile a list of potential candidates, but may also engage, if it deems appropriate, a professional search firm (though it did not do so in 2022). The Nominating and Corporate Governance Committee conducts any appropriate and necessary inquiries into the backgrounds and qualifications of possible candidates after considering the function and needs of the Board. The Nominating and Corporate Governance Committee meets to discuss and consider the candidates' qualifications and then selects a nominee for recommendation to the Board.

The Nominating and Corporate Governance Committee will consider director candidates recommended by stockholders. The Nominating and Corporate Governance Committee evaluates candidates recommended by stockholders in the same manner, including applying the minimum criteria set forth above, as candidates recommended by other sources. Stockholders who wish to recommend individuals for consideration by the

Nominating and Corporate Governance Committee to become nominees for election to the Board may do so by delivering a written recommendation to the Nominating and Corporate Governance Committee as described under "Stockholder Communications with the Board of Directors". Submissions must include the same information required under our Amended and Restated Bylaws for nominating a director.

BOARD DIVERSITY

In addition to the factors discussed above, the Board and the Nominating and Corporate Governance Committee actively seek to achieve a diversity of occupational and personal backgrounds on the Board. The Nominating and Corporate Governance Committee considers a potential director candidate's ability to contribute to the diversity of personal backgrounds on the Board, including with respect to gender, race, ethnic and national background, geography, age and sexual orientation. The Nominating and Corporate Governance Committee assesses its effectiveness in balancing these considerations in connection with its annual evaluation of the composition of the Board. In this regard, our current Board of seven directors includes two directors (28%) who self-identify as female and one director (14%) who self-identifies as racially/ethnically diverse.

In accordance with Nasdaq's board diversity listing standards, we are disclosing aggregated statistical information about our Board's self-identified gender and racial/ethnic characteristics and LGBTQ+ status as voluntarily confirmed to us by each of our directors.

Board Diversity Matrix
(as of April 12)

Total number of directors – 7

Gender identity:	Female	Male	Non-Binary	Did not Disclose Gender
Directors	**2**	**5**	—	—
Number of directors who identify in any of the categories below:				
African American or Black	—	—	—	—
Alaskan Native or Native American	—	—	—	—
Asian	—	**1**	—	—
Hispanic or Latinx	—	—	—	—
Native Hawaiian or Pacific Islander	—	—	—	—
White	**2**	**4**	—	—
Two or More Races or Ethnicities	—	—	—	—
LGBTQ+	—	—	—	—

STOCKHOLDER COMMUNICATIONS WITH THE BOARD OF DIRECTORS

Stockholders and other interested parties may communicate with our Board or a particular director by sending a letter addressed to the Board or a particular director to our Corporate Secretary at the address set forth on the first page of this Proxy Statement. These communications will be compiled and reviewed by our Corporate Secretary, who will determine whether the communication is appropriate for presentation to the Board or the particular director. The purpose of this screening is to allow the Board to avoid having to consider irrelevant or inappropriate communications (such as advertisements, solicitations and hostile communications).

To enable the Company to speak with a single voice, as a general matter, senior management serves as the primary spokesperson for the Company and is responsible for communicating with various constituencies, including stockholders, on behalf of the Company. Directors may participate in discussions with stockholders and other constituencies on issues where Board-level involvement is appropriate. In addition, the Board is kept informed by senior management of the Company's stockholder engagement efforts.

CODE OF ETHICS

The Company has adopted the Protagonist Therapeutics, Inc. Code of Business Conduct and Ethics that applies to all officers, directors and employees. The Code of Business Conduct and Ethics is available in the "Investors — Governance" section of the Company's website at www.protagonist-inc.com. If the Company makes any substantive amendments to the Code of Business Conduct and Ethics or grants any waiver from a provision of the Code to any executive officer or director, the Company intends to promptly disclose the nature of the amendment or waiver on its website, to the extent required by applicable rules.

CORPORATE GOVERNANCE GUIDELINES

The Board has adopted the Corporate Governance Guidelines to serve as a framework for the governance of the Company. The guidelines are also intended to align the interests of directors and management with those of the Company's stockholders. The Corporate Governance Guidelines set forth the Board's practices with respect to board composition and selection, Board diversity, Board meetings, oversight of senior management, Chief Executive Officer performance evaluation and succession planning, and Board committees and compensation. The Corporate Governance Guidelines, as well as the charters for each committee of the Board, may be viewed on the "Investors — Governance" section of the Company's website at www.protagonist-inc.com.

ANTI-HEDGING POLICY

Our insider trading policy prohibits our directors, executive officers and employees from engaging in the trading of derivative securities, short sales, transactions in put or call options, hedging transactions, pledges, holding equity securities in margin accounts or other inherently speculative transactions relating to our equity securities.

ENVIRONMENTAL, SOCIAL AND GOVERNANCE

Environmental, social and governance ("ESG") matters are a priority to us. The Nominating and Corporate Governance Committee oversees this commitment, our ESG initiatives and progress towards related goals and targets. We report on these programs and initiatives, including our drug access and pricing program, our diversity and inclusion priorities, and our community and stakeholder educational efforts related to our therapeutic focus areas. Additional information about our ESG initiatives is available in the "Community" section of the Company's website at www.protagonist-inc.com.

PROPOSAL 2

ADVISORY VOTE ON EXECUTIVE COMPENSATION

Section 14A of the Exchange Act requires that stockholders have the opportunity to cast an advisory (non-binding) vote to approve the compensation of our named executive officers (the "say-on-pay vote").

The say-on-pay vote is a non-binding vote on the compensation of our "named executive officers," as described in this Proxy Statement in the "Executive Compensation" section, the tabular disclosure regarding such compensation and the accompanying narrative disclosure. The say-on-pay vote is not a vote on our general compensation policies or compensation of our Board.

Our philosophy in setting compensation policies for executive compensation is to strongly align our compensation program with stockholder interests, reflect market-best practices, continue to support our long-term business objectives and support talent retention. The "Executive Compensation" section provides a more detailed discussion of our executive compensation program and our compensation philosophy.

The vote under this Proposal 2 is advisory and therefore not binding on us, the Board or our Compensation Committee. However, our Board, including our Compensation Committee, values the opinions of our stockholders and we will consider the outcome of the say-on-pay vote when making future compensation decisions for our named executive officers. We are required to hold the say-on-pay vote at least once every three years, and we have determined to hold a say-on-pay vote every year. Unless the Board modifies its policy on the frequency of holding say-on-pay advisory votes, the next say-on-pay vote is expected to occur in 2024.

THE BOARD OF DIRECTORS RECOMMENDS
A VOTE "FOR" PROPOSAL 2.

PROPOSAL 3

RATIFICATION OF SELECTION OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Audit Committee has selected Ernst & Young LLP as the Company's independent auditor for the fiscal year ending December 31, 2023 and has further directed that management submit the selection of Ernst & Young LLP for ratification by stockholders at the Annual Meeting. Representatives of Ernst & Young LLP are expected to be present at the Annual Meeting. They will have an opportunity to make a statement if they so desire and are expected to be available to respond to appropriate stockholder questions.

Neither the Company's Amended and Restated Bylaws nor other governing documents or law require stockholder ratification of the selection of Ernst & Young LLP as the Company's independent registered public accounting firm. However, the Audit Committee is submitting the selection of Ernst & Young LLP to stockholders for ratification as a matter of good corporate practice. If stockholders fail to ratify the selection, the Audit Committee will reconsider whether or not to retain that firm. Even if the selection is ratified, the Audit Committee in its discretion may direct the appointment of a different independent auditor at any time during the year if it determines that such a change would be in the best interests of the Company and its stockholders.

FEES BILLED BY ERNST & YOUNG LLP DURING FISCAL 2022 AND 2021

The following table summarizes the audit fees billed and expected to be billed by Ernst & Young LLP for the indicated fiscal years and the fees billed by Ernst & Young LLP for all other services rendered during the indicated fiscal years.

	Fiscal Year Ended December 31,	
	2022	2021
Audit Fees[1]	$1,035,150	$1,507,376
Audit-Related Fees[2]	—	—
Tax Fees[3]	20,639	27,605
All Other Fees[4]	3,405	—
Total Fees	$1,059,194	$1,534,981

(1) "Audit Fees" consist of fees billed for professional services rendered for the audit of the Company's consolidated financial statements included in the Company's Annual Report on Form 10-K and for the review of the financial statements included in the Company's Quarterly Reports on Form 10-Q, as well as services as are normally provided by the Company's auditor, including statutory audits and services rendered in connection with statutory and regulatory filings or engagements for the indicated fiscal years, and related expenses. The Audit Fees incurred in 2022 also included fees of $135,000 related to services performed in connection with the Company's at-the-market offerings and a shelf registration statement on Form S-3, including comfort letters, consents and review of documents filed with the SEC. The Audit Fees incurred in 2021 also included fees of $205,000 related to services performed in connection with the Company's at-the-market offerings and a shelf registration statement on Form S-3, including comfort letters, consents and review of documents filed with the SEC.

(2) "Audit-Related Fees" consist of fees billed for assurance and related services by the auditor that are reasonably related to the performance of the audit or review of the Company's financial statements and are not reported under the Audit Fees category.

(3) "Tax Fees" in 2022 and 2021 consist primarily of fees billed for professional services rendered in connection with indirect tax compliance in foreign tax jurisdictions (Australia).

(4) "All Other Fees" consist of fees related to products and services provided by the auditor, other than the services reported above.

All fees described above were pre-approved by the Audit Committee.

PRE-APPROVAL POLICIES AND PROCEDURES

The Audit Committee has adopted policies and procedures for the pre-approval of audit and non-audit services rendered by the Company's independent registered public accounting firm, Ernst & Young LLP. The policy generally allows pre-approval of specified services in the categories of audit services, audit-related

services and tax services, up to specified amounts. Pre-approval may also be given as part of the Audit Committee's approval of the scope of the engagement of the independent auditor or on an individual, explicit, case-by-case basis before the independent auditor is engaged to provide each service. The pre-approval of services may be delegated to one or more of the Audit Committee's members, but the decision must be reported to the full Audit Committee at its next scheduled meeting.

The Audit Committee has determined that the rendering of limited non-audit services by Ernst & Young LLP is compatible with maintaining Ernst & Young LLP's independence.

THE BOARD OF DIRECTORS RECOMMENDS
A VOTE "FOR" PROPOSAL 3.

EXECUTIVE OFFICERS

The following table sets forth certain information with respect to the Company's current executive officers. There are no family relationships among any of our directors or executive officers.

Name	Age	Position
Dinesh V. Patel, Ph.D.	66	President, Chief Executive Officer and Director
Asif Ali	49	Executive Vice President, Chief Financial Officer
Suneel Gupta, Ph.D.	65	Chief Development Officer
Arturo Molina, M.D., M.S., F.A.C.P.	64	Chief Medical Officer

Dinesh V. Patel, Ph.D.

Biographical information for Dr. Patel is included above with the director biographies under the caption "Class I Director Nominee for Election for a Three-Year Term Expiring at the 2026 Annual Meeting."

Asif Ali

Mr. Ali has served as the Company's Executive Vice President, Chief Financial Officer since April 2022. Prior to joining Protagonist, he served as Vice President, Finance and Chief Accounting Officer for Theravance Biopharma, Inc. (Nasdaq: TBPH), a multinational biopharmaceutical company, from September 2018 to February 2022, where he was responsible for equity and asset-backed financings, strategic collaborations, finance operations and long-term business strategy. Prior to Theravance, Mr. Ali served as Vice President and Corporate Controller for Depomed, Inc. (now Assertio Holdings, Inc. (Nasdaq: ASRT)), a specialty pharmaceutical company, from June 2012 to June 2018, where he oversaw and contributed to product launches, product acquisitions and financing projects. From 2010 to 2011, he served as Director of Finance and Accounting for Nevada Property 1 LLC, a former public company that owned and operated the Cosmopolitan of Las Vegas, Nevada. From 2004 to 2009, Mr. Ali worked in public accounting in the life sciences practice of PricewaterhouseCoopers LLP, an accounting firm, where he held various positions of responsibility and left as a Senior Manager. Mr. Ali is a fellow of the Institute of Chartered Accountants in England & Wales, a qualification that he obtained in conjunction with studying accounting at the University of North London, United Kingdom (the combined studies are the U.S. equivalent of a B.S. in Business Administration with concentration in accounting).

Suneel Gupta, Ph.D.

Dr. Gupta has served as the Company's Chief Development Officer since May 2019, and previously, as the Company's Executive Vice President of Clinical Pharmacology and Clinical Operations from January 2019 to May 2019. Prior to joining Protagonist, he was Chief Scientific Officer of Impax Pharmaceuticals, a pharmaceutical company, where he was responsible for all aspects of the company's neurology and psychiatry research and development efforts, including research, development, clinical, regulatory and medical affairs, from 2008 to January 2019. Prior to Impax, Dr. Gupta was Senior Vice President and Distinguished Research Fellow at Johnson & Johnson (NYSE: JNJ), a multinational corporation, where he led early development from 2002 through 2008. Prior to Johnson & Johnson, he held positions at ALZA Corporation, a pharmaceutical and medical systems company, from 1989 through 2001, where he held roles of increasing responsibility, including serving as Vice President of Clinical Pharmacology & Product Discovery. Dr. Gupta serves on the scientific advisory boards of several pharmaceutical companies. Dr. Gupta received a Ph.D. in Pharmacokinetics from the University of Manchester, UK in 1987 and did a postdoctoral fellowship in Clinical Pharmacology at the University of California, San Francisco.

Arturo Molina, M.D., M.S., F.A.C.P.

Dr. Molina has served as the Company's Chief Medical Officer since November 2022. Prior to joining Protagonist, he served as Chief Medical Officer for Sutro Biopharma, Inc. (Nasdaq: STRO), a biotechnology company, where he established a world-class, Cross-Functional Clinical Development, Regulatory, Clinical Operations and Biometrics Team (CDRT) to advance development candidates and optimized leads towards Investigational New Drug and registration-enabling clinical studies, from 2016 to 2022. Prior to Sutro,

Dr. Molina was Vice President, Oncology Scientific Innovation at Johnson & Johnson (NYSE: JNJ), a multinational corporation. Earlier in his career, Dr Molina was Chief Medical Officer at Cougar Biotechnology Inc., until it was acquired by Johnson & Johnson in 2009. Dr. Molina was an Adjunct Professor in the Department of Hematology/Bone Marrow Transplantation at City of Hope Comprehensive Cancer Center, from 2002 to 2004. Prior to that, he served as a faculty staff physician in the Department of Hematology/Bone Marrow Transplantation and Medical Oncology/Therapeutics Research from 1991 to 2002. Dr. Molina received his M.D. and M.S. in Physiology from Stanford University Medical Center, and a B.A. in Psychology and B.S. in Zoology from the University of Texas, Austin. Dr. Molina maintains an Adjunct Clinical Faculty appointment in the Department of Medicine, division of Oncology, Stanford University School Medicine.

SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT

The following table sets forth certain information regarding the ownership of the Company's common stock as of March 15, 2023 by: (i) each director and nominee for director; (ii) each of the named executive officers named in the Summary Compensation Table; (iii) all current executive officers and directors of the Company as a group; and (iv) all persons and entities known by the Company to be beneficial owners of more than five percent of its common stock.

	Beneficial Ownership[1]	
Beneficial Owner	**Number of Shares**	**Percent of Total**
5% Stockholders:		
Farallon Partners, L.L.C. and its affiliated entities[2]	5,151,887	9.7%
Biotechnology Value Fund, L.P. and its affiliated entities[3]	5,025,900	9.5%
State Street Corporation and its affiliated entities[4]	3,792,926	7.4%
BlackRock, Inc.[5]	3,652,157	7.1%
RTW Investments, L.P.[6]	3,591,986	7.0%
The Vanguard Group, Inc.[7]	3,097,714	6.0%
Citadel Advisors LLC and its affiliated entities[8]	2,682,814	5.2%
Named Executive Officers and Directors:		
Dinesh V. Patel, Ph.D.[9]	1,706,580	3.2%
Suneel Gupta, Ph.D.[10]	354,461	*
David Y. Liu, Ph.D.[11]	483,479	*
Harold E. Selick, Ph.D.[12]	153,520	*
Bryan Giraudo[13]	106,500	*
Sarah Noonberg, M.D., Ph.D.[14]	80,100	*
Sarah A. O'Dowd[15]	53,000	*
William D. Waddill[16]	113,475	*
Lewis T. Williams, M.D., Ph.D.[17]	88,500	*
All current executive officers and directors as a group (10 persons)[18]	2,681,916	5.0%

* Represents beneficial ownership of less than one percent of the outstanding common stock.

(1) This table is based upon information supplied by officers, directors and principal stockholders and Schedules 13G filed with the SEC. Beneficial ownership is determined in accordance with the rules promulgated by the SEC. Under such rules, beneficial ownership includes any shares of common stock over which the person or group has sole or shared voting power or investment power as well as any shares of common stock that the person or group has the right to acquire within 60 days after March 15, 2023. Unless otherwise indicated in the footnotes to this table and subject to community property laws where applicable, the Company believes that each of the stockholders named in this table has sole voting and investment power with respect to the shares indicated as beneficially owned. Applicable percentages are based on 51,415,299 shares outstanding on March 15, 2023 adjusted as required by rules promulgated by the SEC. Pursuant to the rules of the SEC, the number of shares of common stock deemed outstanding for a person or group includes shares of common stock such person or group has the right to acquire within 60 days of March 15, 2023. Unless otherwise indicated, the address for each of beneficial owner is c/o Protagonist Therapeutics, Inc., 7707 Gateway Blvd., Suite 140, Newark, California 94560.

(2) This information is based solely upon a Schedule 13G/A filed with the SEC on February 9, 2023 by entities affiliated with Farallon Partners, L.L.C. ("Farallon General Partner"). Consists of (i) 341,600 shares held by Farallon Capital Partners, L.P. ("FCP"), (ii) 263,800 shares held by Farallon Capital Institutional Partners, L.P. ("FCIP"), (iii) 75,600 shares held by Farallon Capital Institutional Partners II, L.P. ("FCIP II"), (iv) 37,400 shares held by Farallon Capital Institutional Partners III, L.P. ("FCIP III"), (v) 50,400 shares held by Four Crossings Institutional Partners V, L.P. ("FCIP V"), (vi) 619,300 shares held by Farallon Capital Offshore Investors II, L.P. ("FCOI II"), (vii) 35,279 shares held by Farallon Capital (AM) Investors, L.P. ("FCAMI"), (viii) 128,370 shares held by Farallon Capital F5 Master I, L.P. ("F5MI"), (ix) 2,100,138 shares held by Farallon Healthcare Partners Master, L.P. ("FHPM," and together with FCP, FCIP, FCIP II, FCIP III, FCIP V, FCOI II, FCAMI and F5MI, the "Farallon Funds") and (x) 1,500,000 shares underlying certain exercisable warrants. Farallon General Partner, as the (i) general partner of each of FCP, FCIP, FCIP II, FCIP III, FCOI II and FCAMI and (ii) the sole member of each of Farallon Institutional (GP) V, L.L.C. ("FCIP

V General Partner") and Farallon Healthcare Partners (GP), L.L.C. ("FHPM General Partner"), is deemed to be the beneficial owner of the shares held by each of the Farallon Funds other than F5MI. FCIP V General Partner, as the general partner of FCIP V, may be deemed to beneficially own the shares held by FCIP V. Farallon F5 (GP), L.L.C. ("F5MI General Partner"), as general partner of F5MI, may be deemed to beneficially own the shares held by F5MI. FHPM General Partner, as general partner of FHPM, may be deemed to beneficially own the shares held by FHPM. Joshua J. Dapice, Philip D. Dreyfuss, Hannah E. Dunn, Michael B. Fisch, Richard B. Fried, Varun N. Gehani, Nicolas Giauque, David T. Kim, Michael G. Linn, Rajiv A. Patel, Thomas G. Roberts, Jr., Edric C. Saito, William Seybold, Daniel S. Short, Andrew J. M. Spokes, John R. Warren and Mark C. Wehrly, each of whom is a managing member or senior managing member of Farallon General Partner, and a manager or senior manager, as the case may be, of FCIP V General Partner, F5MI General Partner and FHPM General Partner, may each be deemed to beneficially own the shares held by the Farallon Funds. The address of each of the entities and persons above is c/o Farallon Capital Management, L.L.C., One Maritime Plaza, Suite 2100, San Francisco, CA 94111.

(3) This information is based solely upon a Schedule 13G filed with the SEC on March 20, 2023 by entities affiliated with Biotechnology Value Fund, L.P. ("BVF"). Consists of (i) 2,053,109 shares held by BVF, (ii) 1,550,785 shares held by Biotechnology Value Fund II, L.P. ("BVF2"), (iii) 156,716 shares held by Biotechnology Value Trading Fund OS LP ("Trading Fund OS"), (iv) 15,290 shares held in certain Partners Managed Accounts, (v) 625,001 shares underlying certain Class A Warrants and (vi) 624,999 shares underlying certain Class B Warrants. BVF I GP LLC ("BVF GP"), as the general partner of BVF, may be deemed to beneficially own the shares beneficially owned by BVF. BVF II GP LLC ("BVF2 GP"), as the general partner of BVF2, may be deemed to beneficially own the shares beneficially owned by BVF2. BVF Partners OS Ltd. ("Partners OS"), as the general partner of Trading Fund OS, may be deemed to beneficially own the shares beneficially owned by Trading Fund OS. BVF GP Holdings LLC ("BVF GPH"), as the sole member of each of BVF GP and BVF2 GP, may be deemed to beneficially own the shares beneficially owned in the aggregate by BVF and BVF2. BVF Partners L.P. ("Partners"), as the investment manager of BVF, BVF2 and Trading Fund OS, and the sole member of Partners OS, may be deemed to beneficially own the shares beneficially owned in the aggregate by BVF, BVF2 and Trading Fund OS, and the shares held in the Partners Managed Accounts. BVF Inc., as the general partner of Partners, may be deemed to beneficially own the shares beneficially owned by Partners. Mark N. Lampert, as a director and officer of BVF Inc., may be deemed to beneficially own the shares beneficially owned by BVF Inc. BVF GP disclaims beneficial ownership of the shares beneficially owned by BVF. BVF2 GP disclaims beneficial ownership of the shares beneficially owned by BVF2. Partners OS disclaims beneficial ownership of the shares beneficially owned by Trading Fund OS. BVF GPH disclaims beneficial ownership of the shares beneficially owned by BVF and BVF2. Each of Partners, BVF Inc. and Mr. Lampert disclaims beneficial ownership of the shares beneficially owned by BVF, BVF2 and Trading Fund OS and held in the Partners Managed Accounts. The address for BVF, BVF GP, BVF2, BVF2 GP, BVF GPH, Partners, BVF Inc. and Mr. Lampert is 44 Montgomery Street, 40th Floor, San Francisco, CA 94104. The address of Trading Fund OS and Partners OS is PO Box 309 Ugland House, Grand Cayman, KY1-1104, Cayman Islands.

(4) This information is based solely upon a Schedule 13G/A filed with the SEC on January 10, 2023 by entities affiliated with State Street Corporation ("State Street"). State Street has shared voting power with respect to 3,706,781 shares and shared dispositive power with respect to 3,792,926 shares. SSGA Funds Management, Inc., as investment advisor, has shared voting power with respect to 2,882,021 shares and shared dispositive power with respect to 2,892,121 shares. Shares are beneficially held by subsidiaries of State Street. The address of State Street and SSGA Funds Management, Inc. is State Street Financial Center, 1 Lincoln Street, Boston, MA 02111.

(5) This information is based solely upon a Schedule 13G/A filed with the SEC on January 31, 2023 by BlackRock, Inc. ("BlackRock"). BlackRock has sole voting power with respect to 3,560,703 shares and sole dispositive power with respect to 3,652,157 shares. The address of BlackRock is 55 East 52nd Street, New York, NY 10055.

(6) This information is based solely upon a Schedule 13G/A jointly filed with the SEC on February 14, 2023 by RTW Investments LP and Roderick Wong. RTW Investments, LP and Mr. Wong have shared voting and dispositive power with respect to 3,591,986 shares directly held by certain funds to which RTW Investments, LP is the investment adviser. Mr. Wong is the Managing Partner and Chief Investment Officer of RTW Investments LP. The address of RTW Investments, LP and Mr. Wong is 40 10th Avenue, Floor 7, New York, NY 10014.

(7) This information is based solely upon a Schedule 13G filed with the SEC on February 9, 2023 by the Vanguard Group, Inc ("Vanguard"). Vanguard has shared voting power with respect to 38,846 shares, sole dispositive power with respect to 3,023,287 shares and shared dispositive power with respect to 74,427 shares. The address of Vanguard is 100 Vanguard Boulevard, Malvern, PA 19355.

(8) This information is based solely upon a Schedule 13G filed with the SEC on January 3, 2023 by entities affiliated with Citadel Advisors LLC ("Citadel Advisors"). Consists of shares held by Citadel Equity Fund Ltd. ("CEFL"), Citadel Multi-Strategy Equities Master Fund Ltd. ("CM"), Citadel Securities LLC ("Citadel Securities") and CRBU Holdings LLC ("CRBH"). Citadel Advisors is the portfolio manager for CEFL and CM. Citadel Advisors Holdings LP ("CAH") is the sole member of Citadel Advisors. Citadel GP LLC ("CGP") is the general partner of CAH. Citadel Securities Group LP ("CALC4") is the non-member manager of Citadel Securities and CRBH. Citadel Securities GP LLC ("CSGP") is the general partner of CALC4. Kenneth Griffin is the President and Chief Executive Officer of CGP, and owns a controlling interest in CGP and CSGP. Each of Citadel Advisors, CAH and CGP has shared voting power and shared dispositive power with respect to 1,783,520 shares. Citadel Securities has shared voting power and shared dispositive power with respect to 502,892 shares. Each of CALC4 and CSGP has shared voting power and shared dispositive power with respect to 899,294 shares. Mr. Griffin has shared voting and shared dispositive power with respect to 2,682,814 shares. The address of each of the entities and persons above is Southeast Financial Center, 200 South Biscayne Boulevard, Suite 3300, Miami, FL 33131.

(9) Includes 1,157,303 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023.

(10) Includes 225,233 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023.

(11) Includes 338,792 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023. Dr. Liu transitioned to a role as part-time R&D Strategy Advisor, effective January 1, 2023.

(12) Includes 138,210 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023.

(13) Includes 18,000 shares held indirectly by the Bryan and Courtney Giraudo Trust and 88,500 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023.

(14) Consists of 80,100 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023. Dr. Noonberg is not standing for re-election at the Annual Meeting.

(15) Consists of 53,000 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023.

(16) Consists of 101,475 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023.

(17) Consists of 88,500 shares issuable pursuant to stock options exercisable within 60 days of March 15, 2023.

(18) Includes 1,988,101 shares that certain executive officers and directors of the Company have the right to acquire within 60 days of March 15, 2023 pursuant to the exercise of outstanding options and vesting of restricted stock units.

EXECUTIVE COMPENSATION

The following table sets forth information regarding compensation awarded to or earned by the executive officers listed below during the years ended December 31, 2022 and 2021.

Our named executive officers ("Named Executive Officers") for 2022, which consist of our principal executive officer and the two most highly compensated executive officers other than the principal executive officer at December 31, 2022 include Dr. Patel, our President and Chief Executive Officer; Dr. Gupta, our Chief Development Officer, and Dr. Liu, our former Chief Research and Development Strategy Officer.

SUMMARY COMPENSATION TABLE FOR FISCAL 2022

Non-Equity Principal Position	Year	Salary ($)[1]	Stock Awards ($)[2][3]	Option Awards ($)[2]	Non-Equity Incentive Plan Compensation ($)[4]	All Other Compensation ($)[5]	Total ($)
Dinesh V. Patel, Ph.D. . . .	2022	630,000	897,813	4,211,963	242,550	10,912	5,993,238
President and Chief Executive Officer	2021	600,000	589,250	3,919,365	429,000	7,118	5,544,733
Suneel Gupta, Ph.D.	2022	500,000	359,125	1,684,785	130,000	10,894	2,684,804
Chief Development Officer	2021	455,000	282,840	1,393,552	236,600	7,118	2,375,110
David Y. Liu, Ph.D.	2022	475,000	287,300	1,347,828	123,500	15,178	2,248,806
Former Chief Research and Development Strategy Officer[6]	2021	455,000	235,700	1,132,261	233,188	14,678	2,070,827

(1) The amounts in the "Salary" column reflect each Named Executive Officer's base salary.

(2) The amounts in the "Stock Awards" and "Option Awards" columns reflect the aggregate grant date fair value of RSUs, performance share awards ("PSUs") and stock options, as applicable, granted during the calendar year and computed in accordance with the provisions of Accounting Standards Codification (ASC) 718, Compensation — Stock Compensation. The valuation methodology of these awards is described in the notes to the Company's financial statements included in its Annual Report on Form 10-K for the year ended December 31, 2022. These amounts do not reflect the actual economic value that will be realized by the Named Executive Officer upon the vesting of the RSUs, PSUs and stock options, the exercise of the stock options, or the sale of the common stock underlying such awards. As required by SEC rules, the amounts shown exclude the impact of estimated forfeitures related to service-based vesting conditions. With respect to option awards only, the Named Executive Officers will only realize compensation to the extent the trading price of the common stock is greater than the exercise price of such stock options.

(3) PSUs granted in 2022 and 2021 were deemed to have no reportable accounting grant date value because the performance goal was not likely to be achieved as of the grant date. The PSUs granted in 2022 vest 100% upon the date that the Compensation Committee determines, in its sole discretion and not later than December 31, 2023, that the Company's forecasted cash and cash equivalents are sufficient to fund the Company's operations through at least December 31, 2025. The PSUs granted in 2021 vest 100% upon the first to occur of a submission of i) a New Drug Application to the U.S. Food and Drug Administration or ii) a European Union marketing authorization for a product candidate. The maximum value of the PSUs at grant date for each of 2022 and 2021, respectively, assuming the performance conditions are achieved is $262,800 and $539,250 for Dr. Patel, $105,120 and $282,840 for Dr. Gupta and $105,120 and $235,700 for Dr. Liu.

(4) The amounts in the "Non-Equity Incentive Plan Compensation" column for 2022 reflect cash bonuses earned for the 2022 fiscal year, which were paid in 2023, based on the achievement of certain predetermined corporate objectives specified by the Board, including operating targets and research and development outcomes. In January 2023, the Compensation Committee determined that the Company met 70% of its 2022 corporate objectives and approved the amount of each Named Executive Officer's bonus. The amount of the bonus that each Named Executive Officer earned for the fiscal year ended on December 31, 2022 is listed in the table below.

Name	2022 Base Salary ($)	Target Bonus (as a% of base salary)	Amount of Bonus Earned ($)
Dinesh V. Patel, Ph.D.	630,000	55%	242,550
Suneel Gupta, Ph.D.	500,000	40%	130,000
David Y. Liu, Ph.D.	475,000	40%	123,500

(5) The amounts noted for 2022 include $6,858 in group term life insurance for Dr. Patel, $6,858 in group term life insurance for Dr. Gupta and $11,124 in group term life insurance for Dr. Liu, and $4,000 in 401(k) plan matching contributions paid by the Company for each of Dr. Patel, Dr. Gupta and Dr. Liu. The amounts for 2022 also include premiums paid for LifeLock identity protection services pursuant to Company-wide policy.

(6) Dr. Liu previously served as our Chief Scientific Officer and Head of Discovery and Clinical Development until January 2022, when he became our Chief Research and Development Strategy Officer. Effective January 1, 2023, Dr. Liu transitioned to a part-time R&D Strategy Advisor. In his new role, Dr. Liu is no longer a Section 16 or executive officer.

NARRATIVE TO SUMMARY COMPENSATION TABLE

EXECUTIVE EMPLOYMENT ARRANGEMENTS WITH NAMED EXECUTIVE OFFICERS

Employment Agreement with Dinesh V. Patel, Ph.D.

In December 2008, the Company entered into an employment agreement with Dinesh V. Patel. Ph.D., the Company's President and Chief Executive Officer, as amended in December 2015, pursuant to which he commenced employment. For 2023, Dr. Patel will receive an annual base salary of $655,200, with an annual target bonus of 55% of that base salary. The amount, if any, of such bonus with respect to any calendar year is based on the achievement of predetermined corporate and personal objectives as determined by the Board in its discretion.

Offer Letter Agreement with Suneel Gupta, Ph.D.

In December 2018, the Company entered into an offer letter agreement with Suneel Gupta, Ph.D., the Company's Chief Development Officer, pursuant to which he commenced employment. For 2023, Dr. Gupta will receive an annual base salary of $515,000, with an annual target bonus of 40% of that base salary. The amount, if any, of such bonus with respect to any calendar year is based on the achievement of predetermined corporate and personal objectives as determined by the Board in its discretion.

Offer Letter Agreement with David Y. Liu, Ph.D.

In May 2013, the Company entered into an offer letter agreement with David Liu, Ph.D., the Company's former Chief Research and Development Strategy Officer (formerly our Chief Scientific Officer and Head of Discovery & Pre-Clinical Development until January 2022), pursuant to which he commenced employment. Effective January 1, 2023, Dr. Liu, transitioned to a part-time R&D Strategy Advisor. In his new role, Dr. Liu is no longer a Section 16 or executive officer.

POTENTIAL PAYMENTS UPON TERMINATION OR CHANGE IN CONTROL

The Company is party to an Employee Severance Agreement with each of its Named Executive Officers and certain of its other executives. If the Company terminates the employee's employment without "cause" or the employee terminates employment for "good reason" (each as defined in the agreement), the employee will receive: (a) salary continuation for 12 months, for the Chief Executive Officer, or nine months, for the other Named Executive Officers (18 months and 12 months, respectively, in the case of a change in control termination); (b) COBRA continuation for the salary continuation period (or an equivalent cash payment if required by law); (c) in the case of a change in control termination only, a monthly payment equal to one twelfth of the target bonus for the severance period; and (d) in the case of a change in control termination only, acceleration of the vesting (and exercisability, if relevant) of equity awards held as of the date of termination. A "change in control termination" is a termination by the Company without "cause" or the employee for "good reason" that occurs within twelve months following the date of a "change in control," as defined in the agreement. Payments and benefits under the agreement are subject to the execution of an effective release.

OUTSTANDING EQUITY AWARDS AT FISCAL YEAR END

The following table shows for the fiscal year ended December 31, 2022, certain information regarding outstanding equity awards at fiscal year end for the Named Executive Officers.

OUTSTANDING EQUITY AWARDS AT DECEMBER 31, 2022

	Option Awards					Stock Awards				
									Equity Incentive Plan Awards:	
	Grant Date	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Option Exercise Price ($)	Vesting Commencement Date	Option Expiration Date	Number of Shares or Units of Stock That Have Not Vested (#)	Market Value of Shares or Units of Stock That Have Not Vested ($)	Number of Unearned Shares, Units or Other Rights That Have Not Vested (#)	Market or Payout Value of Unearned Shares, Units or Other Rights That Have Not Yet Vested ($)
Dinesh V. Patel, Ph.D. . . .	04/29/2016	60,000	—	$ 4.21	04/25/2016	04/28/2026	—	—	—	—
	10/11/2016	320,000	—	$21.58	08/10/2016	10/10/2026	—	—	—	—
	02/28/2018	150,000	—	$16.95	02/28/2018	02/27/2028	—	—	—	—
	08/15/2018	54,700	—	$ 8.58	08/05/2018	08/14/2028	—	—	—	—
	02/28/2019[1][2]	165,312	7,188	$ 8.02	02/28/2019	02/27/2029	7,188	78,421	—	—
	02/28/2020[1]	166,458	68,542	$ 7.80	02/28/2020	02/27/2030	—	—	—	—
	02/26/2021[1][3][4]	103,125	121,875	$23.57	02/26/2021	02/25/2031	25,000	272,750	25,000	272,750
	02/15/2022[1][5]	39,062	148,438	$28.73	02/15/2022	02/14/2032	31,250	340,938	—	—
	05/31/2022[6]	—	—	—	—	—	—	—	30,000	327,300
Suneel Gupta, Ph.D.	01/15/2019[7]	67,708	2,292	$ 7.38	01/07/2019	01/14/2029	—	—	—	—
	02/28/2019[1][2]	43,125	1,875	$ 8.02	02/28/2019	02/27/2029	1,875	20,456	—	—
	02/28/2020[1]	60,208	27,792	$ 7.80	02/28/2020	02/27/2030	—	—	—	—
	02/26/2021[1][3][4]	36,666	43,334	$23.57	02/26/2021	02/25/2031	12,000	130,920	12,000	130,920
	02/15/2022[1][5]	15,625	59,375	$28.73	02/15/2022	02/14/2032	12,000	136,375	—	—
	05/31/2022[6]	—	—	—	—	—	—	—	12,000	130,920
David Y. Liu, Ph.D.	10/11/2016	65,000	—	$21.58	08/10/2016	10/10/2026	—	—	—	—
	02/28/2018	56,500	—	$16.95	02/28/2018	02/27/2028	—	—	—	—
	08/15/2018	17,200	—	$ 8.58	08/05/2018	08/14/2028	—	—	—	—
	02/28/2019[1][2]	86,250	3,750	$ 8.02	02/28/2019	02/27/2029	3,750	40,913	—	—
	02/28/2020[1]	49,583	20,417	$ 7.80	02/28/2020	02/27/2030	—	—	—	—
	02/26/2021[1][3][4]	29,791	35,209	$23.57	02/26/2021	02/25/2031	10,000	109,100	10,000	109,100
	02/15/2022[1][5]	12,500	47,500	$28.73	02/15/2022	02/14/2032	10,000	109,100	—	—
	05/31/2022[6]	—	—	—	—	—	—	—	12,000	130,920

(1) The shares subject to the option vest as to 1/48 of the shares in equal monthly installments following the vesting commencement date, subject to the holder continuing to provide services through the applicable vesting date. The option is subject to accelerated vesting in the event of an acquisition and in the event of a qualifying termination that occurs in the twelve months following the acquisition as described in "— Potential Payments upon Termination or Change in Control" above.

(2) 25% of the stock award shares vest in equal yearly installments over four years subject to the holder continuing to provide services through the applicable vesting date. The award is subject to accelerated vesting in the event of an acquisition and in the event of a qualifying termination that occurs in the twelve months following the acquisition as described in "— Potential Payments upon Termination or Change in Control" above.

(3) 100% of the stock award vests three years from the grant date subject to the holder continuing to provide services through the applicable vesting date. The award is subject to accelerated vesting in the event of an acquisition and in the event of a qualifying termination that occurs in the twelve months following the acquisition as described in "— Potential Payments upon Termination or Change in Control" above.

(4) 100% of the equity incentive plan award vests upon the first to occur of a submission of i) a New Drug Application to the U.S. Food and Drug Administration or ii) a European Union marketing authorization for a product candidate, subject to the holder continuing

to provide services through the applicable vesting date. The award is subject to accelerated vesting in the event of an acquisition and in the event of a qualifying termination that occurs in the twelve months following the acquisition as described in "— Potential Payments upon Termination or Change in Control" above.

(5) 1/3 of the stock award shares vest in equal yearly installments over three years subject to the holder continuing to provide services through the applicable vesting date. The award is subject to accelerated vesting in the event of an acquisition and in the event of a qualifying termination that occurs in the twelve months following the acquisition as described in "— Potential Payments upon Termination or Change in Control" above.

(6) 100% of the equity incentive plan award vests upon the date that the Compensation Committee determines in its sole discretion and not later than December 31, 2023, that the Company's forecasted cash and cash equivalents are sufficient to fund the Company's operations through at least December 31, 2025, subject to the holder continuing to provide services through the applicable vesting date. The award is subject to accelerated vesting in the event of an acquisition and in the event of a qualifying termination that occurs in the twelve months following the acquisition as described in "— Potential Payments upon Termination or Change in Control" above.

(7) 25% of the shares subject to the option vest on the first anniversary of the vesting commencement date, and the remainder vests in 36 equal monthly installments thereafter, subject to the holder continuing to provide services through the applicable vesting date. The option is subject to accelerated vesting in the event of an acquisition and in the event of a qualifying termination that occurs in the twelve months following the acquisition as described in "— Potential Payments upon Termination or Change in Control" above.

NONQUALIFIED DEFERRED COMPENSATION

The Company does not maintain any nonqualified deferred compensation plans. The Board may elect to provide the Company's officers and other employees with nonqualified deferred compensation benefits in the future if it determines that doing so is in the Company's best interests.

401(K) PLAN

The Company maintains a tax-qualified retirement plan that provides eligible U.S. employees with an opportunity to save for retirement on a tax advantaged basis. Eligible employees may defer eligible compensation subject to applicable annual Internal Revenue Code of 1986, as amended (the "Code"), limits. The 401(k) plan permits participants to make both pre-tax and certain after-tax (Roth) deferral contributions. These contributions are allocated to each participant's individual account and are then invested in selected investment alternatives according to the participant's directions. Employees are immediately and fully vested in their contributions. The Company may make contributions to this plan at its discretion. For the years ended December 31, 2022 and 2021, the Company matched 50% of each employee's contribution up to a maximum of $4,000 and $3,500, respectively. The 401(k) plan is intended to be qualified under Section 401(a) of the Code with the 401(k) plan's related trust intended to be exempt under Section 501(a) of the Code. As a tax qualified retirement plan, contributions to the 401(k) plan and earnings on those contributions are not taxable to the employees until distributed from the 401(k) plan.

PAY VERSUS PERFORMANCE

As required by Section 953(a) of the Dodd-Frank Wall Street Reform and Consumer Protection Act, and Item 402(v) of Regulation S-K, we are providing the following information about the relationship between executive compensation actually paid and certain financial performance of the Company.

Year	Summary Compensation Table Total for PEO[1]	Compensation Actually Paid to PEO[2]	Average Summary Compensation Table Total for Non-PEO NEOs[3]	Average Compensation Actually Paid to Non-PEO NEOs[4]	Value of Initial Fixed $100 Investment Based On Total Shareholder Return[5]	Net Loss[6]
2022	$5,993,238	$ (5,174,369)	$2,466,805	$(1,687,548)	$ 54.12	$(127,393,315)
2021	$5,544,733	$12,111,993	$2,222,969	$ 4,761,991	$169.64	$(125,550,748)

(1) The dollar amounts reported are the amounts of total compensation reported in our Summary Compensation Table for each of 2022 and 2021 for Dr. Patel, our President and Chief Executive Officer.

(2) The dollar amounts reported represent the amount of "compensation actually paid", as computed in accordance with SEC rules. The dollar amounts do not reflect the actual amount of compensation earned by or paid during the applicable year. In accordance with SEC rules, the following adjustments were made to total compensation to determine the compensation actually paid:

Year	Reported Summary Compensation Table Total for PEO	Reported Value of Equity Awards[(a)]	Equity Award Adjustments[(b)]	Compensation Actually Paid to PEO
2022	$5,993,238	$(5,109,776)	$ (6,057,831)	$ (5,174,369)
2021	$5,544,733	$(4,508,615)	$11,075,875	$12,111,993

(a) The grant date fair value of equity awards represents the total of the amounts reported in the "Stock Awards" and "Option Awards" columns in the Summary Compensation Table for the applicable year.

(b) The equity award adjustments for each applicable year include the addition (or subtraction, as applicable) of the following: (i) the year-end fair value of any equity awards granted in the applicable year that are outstanding and unvested as of the end of the year; (ii) the amount of change as of the end of the applicable year (from the end of the prior fiscal year) in fair value of any awards granted in prior years that are outstanding and unvested as of the end of the applicable year; (iii) for awards that are granted and vest in same applicable year, the fair value as of the vesting date; (iv) for awards granted in prior years that vest in the applicable year, the amount equal to the change as of the vesting date (from the end of the prior fiscal year) in fair value; (v) for awards granted in prior years that are determined to fail to meet the applicable vesting conditions during the applicable year, a deduction for the amount equal to the fair value at the end of the prior fiscal year; and (vi) the dollar value of any dividends or other earnings paid on stock or option awards in the applicable year prior to the vesting date that are not otherwise reflected in the fair value of such award or included in any other component of total compensation for the applicable year. The valuation assumptions used to calculate fair values did not materially differ from those disclosed at the time of grant. The amounts deducted or added in calculating the equity award adjustments are as follows:

Year	Year End Fair Value of Outstanding and Unvested Equity Awards Granted During the Year	Year over Year Change in Fair Value of Outstanding and Unvested Equity Awards Granted in Prior Years	Fair Value as of Vesting Date of Equity Awards Granted and Vested in the Year	Year over Year Change in Fair Value of Equity Awards Granted in Prior Years that Vested in the Year	Total Equity Award Adjustments
2022	$1,538,304	$(4,758,042)	$ 328,901	$(3,166,994)	$ (6,057,831)
2021	$5,481,885	$ 2,690,740	$1,252,857	$ 1,650,393	$11,075,875

(3) The dollar amounts reported represent the average of the amounts reported for the Company's named executive officers (NEOs) as a group (excluding our CEO) in the "Total" column of the Summary Compensation Table in each applicable year. The names of each of the NEOs (excluding our CEO) included for purposes of calculating the average amounts in 2022 and 2021 are Suneel Gupta, Ph.D. and David Y. Liu, Ph.D.

(4) The dollar amounts reported represent the average amount of "compensation actually paid" to the NEOs as a group (excluding our CEO), as computed in accordance with SEC rules. The dollar amounts do not reflect the actual average amount of compensation earned by or paid to the NEOs as a group (excluding our CEO) during the applicable year. In accordance with the SEC rules, the following adjustments were made to average total compensation for the NEOs as a group (excluding our CEO) for each year to determine the compensation actually paid, using the same methodology described above in Note 2:

Year	Average Reported Summary Compensation Table Total for Non-PEO NEOs	Average Reported Value of Equity Awards	Average Equity Award Adjustments[(a)]	Average Compensation Actually Paid to Non-PEO NEOs
2022	$2,466,805	$(1,839,519)	$(2,314,834)	$(1,687,548)
2021	$2,222,969	$(1,522,177)	$ 4,061,199	4,761,991

(a) The amounts deducted or added in calculating the total average equity award adjustments are as follows:

Year	Average Year End Fair Value of Outstanding and Unvested Equity Awards Granted During the Year	Year over Year Average Change in Fair Value of Outstanding and Unvested Equity Awards Granted in Prior Years	Average Fair Value as of Vesting Date of Equity Awards Granted and Vested in the Year	Year over Year Average Change in Fair Value of Equity Awards Granted in Prior Years that Vested in the Year	Total Average Equity Award Adjustments
2022	$ 553,787	$(1,661,551)	$118,408	$(1,325,478)	$(2,314,834)
2021	$1,867,101	1,110,914	$403,689	$ 679,495	$ 4,061,199

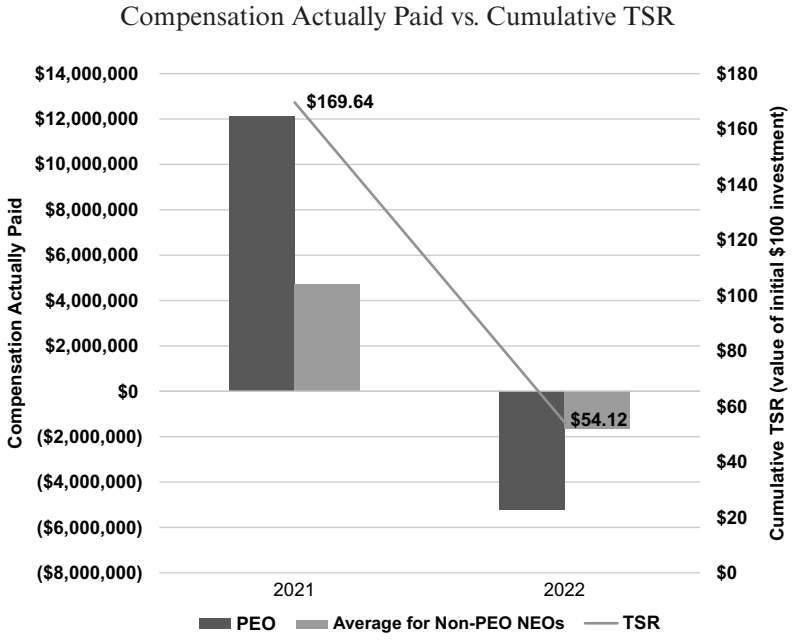
(5) Cumulative TSR is calculated by dividing the sum of the cumulative amount of dividends for the measurement period, assuming dividend reinvestment, and the difference between the Company's share price at the end and the beginning of the measurement period by the Company's share price at the beginning of the measurement period.

(6) The dollar amounts reported represent the amount of net loss reflected in the Company's audited financial statements for the applicable year.

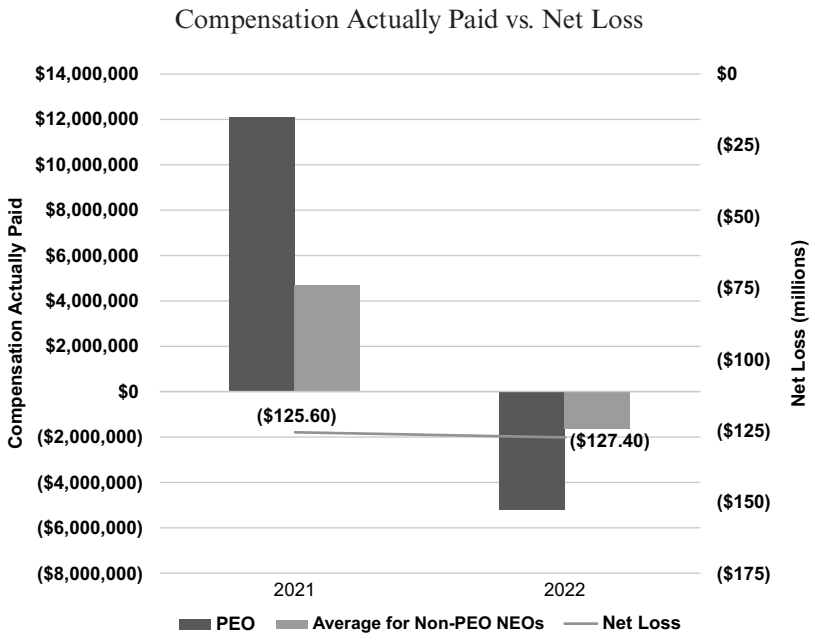
Analysis of the Information Presented in the Pay versus Performance Table

The Company's executive compensation program reflects a variable pay-for-performance philosophy. While the Company utilizes several performance measures to align executive compensation with Company performance, all of those Company measures are not presented in the Pay versus Performance table. Moreover, the Company generally seeks to incentivize long-term performance, and therefore does not specifically align the Company's performance measures with compensation that is actually paid (as computed in accordance with SEC rules) for a particular year. In accordance with SEC rules, the Company is providing the following graphs depicting the relationships between information presented in the Pay versus Performance table.

Compensation Actually Paid and Cumulative TSR



Compensation Actually Paid and Net Loss



DIRECTOR COMPENSATION

The following table shows for the fiscal year ended December 31, 2022 certain information with respect to the compensation of all non-employee directors of the Company:

NON-EMPLOYEE DIRECTOR COMPENSATION FOR FISCAL 2022

Name	Fees Earned or Paid in Cash ($)	Option Awards ($)[1][2]	Total ($)
Bryan Giraudo	60,000	128,940	188,940
Sarah Noonberg, M.D., Ph.D.	50,000	128,940	178,940
Sarah A. O'Dowd	45,000	128,940	173,940
Harold E. Selick, Ph.D.	95,000	128,940	223,940
William D. Waddill	67,500	128,940	196,440
Lewis T. Williams, M.D., Ph.D.	47,500	128,940	176,440

(1) The amounts in the "Option Awards" column reflect the aggregate grant date fair value of stock options granted during the calendar year computed in accordance with the provisions of Accounting Standards Codification (ASC) 718, Compensation — Stock Compensation. The valuation assumptions used in determining such amounts are described in the notes to the Company's financial statements included in its Annual Report on Form 10-K for the year ended December 31, 2022. These amounts do not reflect the actual economic value that will be realized by the directors upon the vesting of the stock options, the exercise of the stock options, or the sale of the common stock underlying such stock options.

(2) The aggregate number of stock option awards for each non-employee director that were outstanding as of the end of fiscal year 2022 is shown in the table below. Our non-employee directors did not hold any other outstanding stock awards as of such date.

Name	Aggregate Number of Option Awards Outstanding as of December 31, 2022
Bryan Giraudo	101,000
Sarah Noonberg, M.D., Ph.D.	92,600
Sarah A. O'Dowd	68,000
Harold E. Selick, Ph.D.	150,710
William D. Waddill	113,975
Lewis T. Williams, M.D. Ph.D.	101,000

In September 2016, the Board adopted a non-employee director compensation policy. The Compensation Committee made certain changes to the non-employee director compensation policy effective as of January 1, 2020 and May 16, 2022 (increasing the number of options granted as part of the annual equity award from 18,000 to 20,000). Pursuant to this policy, the Company compensates its non-employee directors with a combination of cash and equity. The annual cash compensation contained in this policy, set forth below, is payable in equal quarterly installments, in advance during the last month of each quarter in which service occurred, prorated for any months of partial service.

- Annual Board Service Retainer:
  - Non-employee directors other than the non-executive chairperson: $40,000
  - Non-executive chairperson: $75,000
- Annual Committee Service Retainer (Chairperson):
  - Chairperson of the Audit Committee: $20,000

- Chairperson of the Compensation Committee: $15,000
- Chairperson of the Nominating and Corporate Governance Committee: $10,000

- Annual Committee Service Retainer (Non-Chairperson):
  - Audit Committee: $10,000
  - Compensation Committee: $7,500
  - Nominating and Corporate Governance Committee: $5,000

The Company's non-employee director compensation policy also provides for equity compensation to each non-employee director as follows:

- Initial Grant: At the time he or she joins the Board, each new non-employee director will receive an initial stock option grant to purchase 30,000 shares of common stock and shall vest in equal monthly installments over three years.
- Annual Grant: Each non-employee director will also be granted an option to purchase 20,000 shares of common stock on the date of each Annual Meeting of stockholders which shall vest at the earlier of (i) one year or (ii) the next Annual Meeting of stockholders.

All options granted to the Company's non-employee directors under the policy will vest in full upon the completion of a change in control.

NON-EMPLOYEE DIRECTOR COMPENSATION FOR FISCAL 2023

After consultation with Radford and pursuant to the compensation review process described above, effective January 1, 2023, the number of shares subject to the annual option grant to be awarded in fiscal year 2023 to non-employee directors was increased to 30,000 shares. The annual option grant to non-employee directors shall be granted on the same day as the annual employee refresher awards and shall vest in equal monthly installments over twelve months.

EQUITY COMPENSATION PLAN INFORMATION

The following table provides certain information with respect to all of the Company's equity compensation plans in effect as of December 31, 2022.

Plan Category[1]	Number of securities to be issued upon exercise of outstanding options, warrants and rights (a)	Weighted average exercise price of outstanding options, warrants and rights[6] (b)	Number of securities remaining available for issuance under equity compensation plans (excluding securities reflected in column (a)) (c)
Equity compensation plans approved by securities holders:			
2007 Stock Option and Incentive Plan	167,828[3]	$ 3.78	—
2016 Equity Incentive Plan	5,914,150[4]	$19.20	1,350,793[7]
2016 Employee Stock Purchase Plan	—	—	1,255,290[8]
Equity compensation plans not approved by securities holders:			
2018 Inducement Plan[2]	995,467[5]	$20.85	574,772
Total	7,077,445	$19.03	3,180,855

(1) The equity compensation plans are described in Note 13 to our financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2022.

(2) In February 2020, the Board approved the Amended and Restated 2018 Inducement Plan, a non-stockholder approved stock plan, under which it reserved and authorized up to 1,250,000 shares of the Company's common stock in order to award options and RSUs to persons that were not previously employees or directors of the Company, or following a bona fide period of non-employment, as an inducement material to such persons entering into employment with the Company, within the meaning of Rule 5635(c)(4) of the Nasdaq Listing Rules. The Board approved a further amendment and restatement in February 2022 to reserve and authorize an additional 500,000 shares of the Company's common stock thereunder (as amended and restated in February 2022, the "2018 Inducement Plan"). The 2018 Inducement Plan is administered by the Board or the Compensation Committee of the Board, which determines the types of awards to be granted, including the number of shares subject to the awards, the exercise price and the vesting schedule. Awards granted under the 2018 Inducement Plan expire no later than ten years from the date of grant.

(3) As of December 31, 2022, there were 167,828 shares of common stock subject to outstanding stock options under the 2007 Stock Option and Incentive Plan.

(4) As of December 31, 2022, there were 5,123,464 shares of common stock subject to outstanding stock options, 709,186 shares to be issued pursuant to the vesting of unvested RSUs, and 81,500 shares to be issued pursuant to the vesting of unvested PSUs upon achievement of performance conditions under the 2016 Equity Incentive Plan (the "2016 Plan").

(5) As of December 31, 2022, there were 949,217 shares of common stock subject to outstanding stock options and 46,250 shares to be issued pursuant to the vesting of unvested RSUs under the 2018 Inducement Plan.

(6) The weighted-average exercise price of outstanding stock options granted under equity compensation plans approved by securities holders was $18.71. The weighted-average exercise price of outstanding options granted under all equity compensation plans was $19.03. RSUs and PSUs do not have an exercise price and therefore have not been included in the calculations.

(7) The reserve for shares available under the 2016 Plan will automatically increase on January 1st each year by an amount equal to 4 percent of the total number of outstanding shares of our capital stock on December 31st of the preceding fiscal year, or a lesser number of shares determined by the Board. Shares subject to stock awards granted under our 2016 Plan that expire or cancel without being exercised in full, or that are paid out in cash rather than in shares, do not reduce the number of shares available for issuance under our 2016 Plan. Additionally, shares issued pursuant to stock awards under our 2016 Plan that we repurchase or that are forfeited, as well as shares used to pay the exercise price of a stock award or to satisfy the tax withholding obligations related to a stock award, become available for future grant under our 2016 Plan.

(8) The reserve for shares available under the 2016 Employee Stock Purchase Plan (the "2016 ESPP") will automatically increase on January 1st each year by the lesser of: (i) one percent of the total number of outstanding shares of our capital stock outstanding on December 31st of the preceding fiscal year, (ii) 300,000 shares, or (iii) such other number of shares determined by the Board. As of December 31, 2022, an aggregate of 1,255,290 shares remained available for future issuance under the 2016 ESPP, including 68,605 shares subject to purchase during the purchase period in effect on December 31, 2022.

TRANSACTIONS WITH RELATED PERSONS AND INDEMNIFICATION

RELATED-PERSON TRANSACTIONS POLICY AND PROCEDURES

The Company has adopted a written Related-Person Transactions Policy that sets forth the Company's policies and procedures regarding the identification, review, consideration and approval or ratification of "related-persons transactions." For purposes of the Company's policy only, a "related-person transaction" is a transaction, arrangement or relationship (or any series of similar transactions, arrangements or relationships) in which the Company and any "related person" are participants involving an amount that exceeds $120,000. Transactions involving compensation for services provided to the Company as an employee, director, consultant or similar capacity by a related person are not covered by this policy. A related person is any executive officer, director, or more than 5% stockholder of the Company, including any of their immediate family members, and any entity owned or controlled by such persons.

CERTAIN RELATED-PERSON TRANSACTIONS

The following is a summary of transactions since January 1, 2021 in which the Company participated, in which the amount involved exceeded or will exceed $120,000, and in which any of the Company's directors, executive officers or beneficial owners of more than 5% of the Company's common stock or any members of their immediate family had or will have a direct or indirect material interest, other than compensation arrangements which are described under "Executive Compensation" and "Director Compensation."

2018 OFFERING

On August 6, 2018, the Company entered into a securities purchase agreement (the "Securities Purchase Agreement") with certain accredited investors, including entities affiliated with Biotechnology Value Fund, L.P. (collectively, "BVF") and entities affiliated with Farallon Partners, LLC, each a holder of more than 5% of the Company's common stock, relating to the issuance and sale of 2,750,000 shares of the Company's common stock at a negotiated purchase price of $8.00 per share, for aggregate net proceeds of $21.7 million, after deducting offering expenses payable by us. In concurrent private placements, the Company issued such investors warrants to purchase an aggregate of 2,750,000 shares of the Company's common stock (each, a "Warrant" and, collectively, the "Warrants"). Each Warrant is exercisable from August 8, 2018 through August 8, 2023. Warrants to purchase 1,375,000 shares of the Company's common stock have an exercise price of $10.00 per share ("Class A Warrants") and Warrants to purchase 1,375,000 shares of the Company's common stock have an exercise price of $15.00 per share ("Class B Warrants"). The exercise price and number of shares of common stock issuable upon the exercise of the Warrants (the "Warrant Shares") are subject to adjustment in the event of any stock dividends and splits, reverse stock split, recapitalization, reorganization or similar transaction, as described in the Warrants. Under certain circumstances, the Warrants may be exercisable on a "cashless" basis. As of December 31, 2022, none of the Warrants have been exercised.

In connection with the issuance and sale of the common stock and Warrants, the Company granted the investors certain registration rights with respect to the Warrants and the Warrant Shares.

WARRANT EXCHANGE

On December 21, 2018, the Company entered into an exchange agreement with entities affiliated with BVF (the "Exchanging Stockholders"), pursuant to which the Company exchanged an aggregate of 1,000,000 shares of common stock owned by the Exchanging Stockholders for pre-funded warrants (the "Exchange Warrants") to purchase an aggregate of 1,000,000 shares of common stock (subject to adjustment in the event of stock splits, recapitalizations and other similar events affecting common stock), with an exercise price of $0.00001 per share. The Exchange Warrants expire ten years from the date of issuance. The Exchange Warrants are exercisable at any time prior to expiration except that the Exchange Warrants cannot be exercised by the Exchanging Stockholders if, after giving effect thereto, the Exchanging Stockholders would beneficially own more than 9.99% of the Company's common stock, subject to certain exceptions. The holders of the Exchange Warrants will not have the right to vote on any matter except to the extent required by Delaware law. The Exchange Warrants were issued without registration under the Securities Act in reliance on the exemption from registration contained in Section 3(a)(9) of the Securities Act. During the year ended December 31, 2019, Exchange Warrants to purchase 600,000 shares were net exercised, resulting in the issuance of

599,997 shares of common stock. During the year ended December 31, 2022, Exchange Warrants to purchase 400,000 shares were net exercised, resulting in the issuance of 399,997 shares of common stock. As of December 31, 2022, there were no outstanding Exchange Warrants.

INDEMNIFICATION

The Company provides indemnification for its directors and executive officers so that they will be free from undue concern about personal liability in connection with their service to the Company. Under the Company's Amended and Restated Bylaws, the Company is required to indemnify its directors and executive officers to the extent not prohibited under Delaware or other applicable law. The Company has also entered into indemnity agreements with certain officers and directors. These agreements provide, among other things, that the Company will indemnify the officer or director, under the circumstances and to the extent provided for in the agreement, for expenses, damages, judgments, fines and settlements he or she may be required to pay in actions or proceedings which he or she is or may be made a party by reason of his or her position as a director, officer or other agent of the Company, and otherwise to the fullest extent permitted under Delaware law and the Amended and Restated Bylaws.

HOUSEHOLDING OF PROXY MATERIALS

The SEC has adopted rules that permit companies and intermediaries (e.g., brokers) to satisfy the delivery requirements for Notices of Internet Availability of Proxy Materials or other Annual Meeting materials with respect to two or more stockholders sharing the same address by delivering a single Notice of Internet Availability of Proxy Materials or other Annual Meeting materials addressed to those stockholders. This process, which is commonly referred to as "householding," potentially means extra convenience for stockholders and cost savings for companies.

This year, a number of brokers with account holders who are Protagonist stockholders will be "householding" the Company's proxy materials. A single Notice of Internet Availability of Proxy Materials will be delivered to multiple stockholders sharing an address unless contrary instructions have been received from the affected stockholders. Once you have received notice from your broker that they will be "householding" communications to your address, "householding" will continue until you are notified otherwise or until you revoke your consent. If, at any time, you no longer wish to participate in "householding" and would prefer to receive a separate Notice of Internet Availability of Proxy Materials, please notify your broker or Protagonist, and we will promptly deliver a separate Notice of Internet Availability of Proxy Materials to you. Direct your written request to Protagonist Therapeutics, Inc., c/o Matthew Gosling, Executive Vice President, General Counsel, at 7707 Gateway Blvd., Suite 140, Newark, California 94560 or contact Matthew Gosling at (510) 474-0932. Stockholders who currently receive multiple copies of the Notices of Internet Availability of Proxy Materials at their addresses and would like to request "householding" of their communications should contact their brokers.

We will provide a copy of the Company's Annual Report on Form 10-K for the year ended December 31, 2022 without charge upon the written or oral request of a stockholder. Please send a written request to: Corporate Secretary, Protagonist Therapeutics, Inc., 7707 Gateway Blvd., Suite 140, Newark, California 94560 or call 510-474-0170.