Table of Contents

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, 2021

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. Yes ☐ No ☐

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 $2.1 billion as of June 30, 2021, based upon the closing sale price on The Nasdaq Stock Market LLC reported on June 30, 2021. Excludes an aggregate of 528,731 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, 2021, the registrant assumed that a stockholder was an affiliate of the registrant at June 30, 2021 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, 2021. 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 48,413,555 shares of registrant's Common Stock, par value $0.00001 per share, outstanding as of February 15, 2022.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant's definitive Proxy Statement for the registrant's 2022 Annual Meeting of Stockholders, to be filed subsequent to the date hereof with the Securities and Exchange Commission ("SEC"), are incorporated by reference into Part III of this report. Such proxy statement will be filed with the SEC not later than 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:	Redwood City, California, USA

PROTAGONIST THERAPEUTICS, INC.
2021 FORM 10-K ANNUAL REPORT
TABLE OF CONTENTS

		Page
PART I		
Item 1.	Business	4
Item 1A.	Risk Factors	29
Item 1B.	Unresolved Staff Comments	52
Item 2.	Properties	52
Item 3.	Legal Proceedings	52
Item 4.	Mine Safety Disclosures	52
PART II		
Item 5.	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	53
Item 6.	Reserved	55
Item 7.	Management's Discussion and Analysis of Financial Condition and Results of Operations	55
Item 7A.	Quantitative and Qualitative Disclosures about Market Risk	72
Item 8.	Financial Statements and Supplementary Data	73
Item 9.	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	112
Item 9A.	Controls and Procedures	112
Item 9B.	Other Information	114
Item 9C.	Disclosure Regarding Foreign Jurisdictions that Prevent Inspections	114
PART III		
Item 10.	Directors, Executive Officers, and Corporate Governance	115
Item 11.	Executive Compensation	115
Item 12.	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	115
Item 13.	Certain Relationships and Related Transactions, and Director Independence	115
Item 14.	Principal Accounting Fees and Services	115
PART IV		
Item 15.	Exhibits, Financial Statement Schedules	116
Item 16.	Form 10-K Summary	120
SIGNATURES		121

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," "could," "potentially" or the negative of these terms or similar expressions. You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other "forward-looking" information. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements are subject to certain risks and uncertainties 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 beliefs 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 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.

Under "**Risks Related to the COVID-19 Pandemic**" we describe risks to our business arising from the COVID-19 pandemic. The pandemic has and could continue to adversely impact our business, including our ongoing and planned clinical trials and preclinical and discovery research. The impacts on our business include, among others, delays to some of our ongoing clinical trials.

Under "**Risks Related to Clinical Development**" we describe risks related to on our ongoing clinical development efforts. They include, among others, the following:

- We have no approved products and no historical product 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.

Under "**Risks Related to Financial Position and Capital Requirements**" we describe risks associated with our financial position and future capital requirements. They include, among others, the following:

- 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.

Under "**Risks Related to Our Reliance on Third Parties**" we describe risks related to our reliance on third parties. They include, among others, the following:

- 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.

Under "**Risks Related to Regulatory Approval**" we describe risks related to the potential regulatory approval required to market our product candidates in the United States or other jurisdictions. If we are ultimately unable to obtain regulatory approval for our product candidates, our business will be substantially harmed.

Under "**Risks Related to Commercialization of our Product Candidates**" we describe risks related to the commercialization of any of our product candidates that are eventually approved for marketing. 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. Also, if we commercialize our product candidates abroad, we will be subject to the risks of doing business outside of the United States.

Under "**Risks Related to Our Business and Industry**" we describe risks related to our business in general, and to our company in the biotechnology and pharmaceutical industry. They include, among others, the following:

- We face significant competition from other biotechnology and pharmaceutical companies.
- 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.

Under "**Risks Related to Our Intellectual Property**" we describe risks related to the intellectual property that is critical to the success of our business. They include, among others, the following:

- 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.

Under "**Risks Related to Ownership of our Common Stock**" we describe risks associated with owning our common stock. They include, among others, the following:

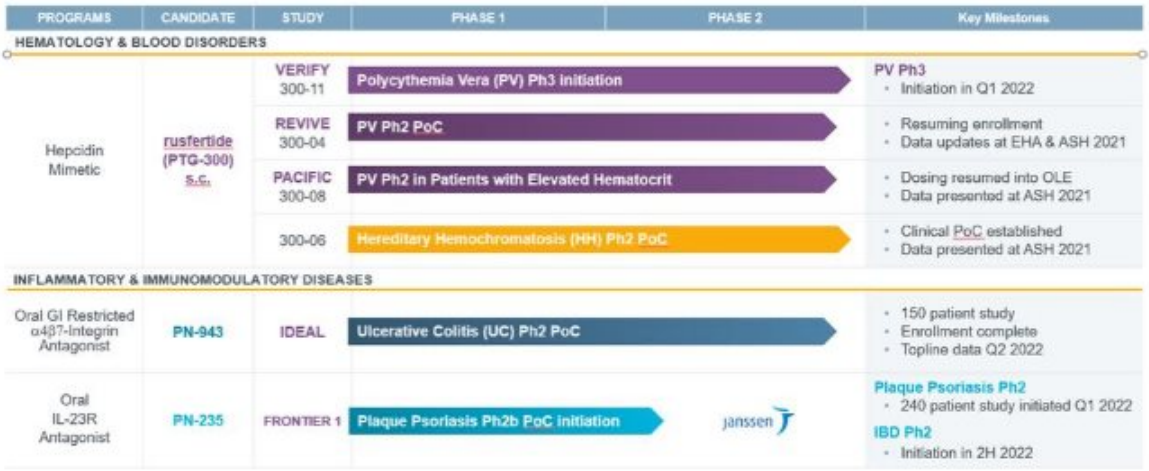
- Our stock price has been and will likely continue to be volatile and may decline, regardless of our operating performance.
- Any failure to maintain the adequacy of internal controls may adversely affect investor confidence in our company and, as a result, the value of our common stock.
- Some provisions of our charter documents and Delaware law may have anti-takeover effects that could discourage an acquisition of us by others, or make it difficult for stockholders to replace members of our board of directors.

Item 1. Business

Overview

We are a biopharmaceutical company with multiple peptide-based new chemical entities in different stages of development, all derived from the Company's proprietary technology platform. Our clinical programs address two broad categories of diseases; (i) hematology and blood disorders, and (ii) inflammatory and immunomodulatory diseases.

Figure 1: Our Product Pipeline



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. 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. We initiated REVIVE, a Phase 2 proof of concept ("POC") study in the blood disorder polycythemia vera ("PV"), in the third quarter of 2019. We initiated a Phase 2 POC study in hereditary hemochromatosis ("HH") in January 2020, which was completed during the fourth quarter of 2021. During the first quarter of 2021, we initiated PACIFIC, another Phase 2 study for rusfertide in up to 20 patients diagnosed with PV and with routinely elevated hematocrit levels (>48%).

In June 2021, we presented updated Phase 2 data supporting the long-term efficacy of rusfertide in PV during an oral presentation at the European Hematology Association ("EHA") 2021 Virtual Congress. An abstract highlighting positive preliminary data from our Phase 2 study of rusfertide in HH was orally presented at The Liver Meeting® 2021, hosted by the American Association for the Study of Liver Diseases ("AASLD"), which took place virtually in November 2021. In December 2021, two abstracts highlighting positive updated data from our REVIVE and PACIFIC Phase 2 studies of rusfertide in PV were orally presented at the American Society of Hematology ("ASH") 2021 Annual Meeting, in addition to three poster presentations on rusfertide in PV and HH. These results 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 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.

On September 16, 2021, the FDA placed a clinical hold on our rusfertide clinical studies 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 clinical study protocols of 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.

We enrolled 63 patients in the ongoing REVIVE Phase 2 clinical trial of rusfertide in PV prior to the clinical hold, and we are currently enrolling approximately 20 patients to target approximately 50 patients enrolled through the end of a three-year open label extension ("OLE"). Based on ongoing end of Phase 2 feedback provided by the FDA's Division of Nonmalignant Hematology and written comments from the European Medicines Agency ("EMA"), we expect to initiate VERIFY, a global Phase 3 clinical trial of rusfertide in PV in the first quarter of 2022. Patient enrollment into VERIFY is expected to be completed in the first half of 2023. In addition, we completed our Phase 2 POC study in HH, our second indication, during the fourth quarter of 2021.

To date we have received 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;
- The FDA granted Fast Track designation for rusfertide for the treatment of PV in December 2020; and
- The FDA granted Breakthrough Therapy Designation for rusfertide for the treatment of PV in June 2021.

Our alpha-4-beta-7 ("α4β7") antagonist PN-943 and our Interleukin-23 receptor ("IL-23R") antagonist compound PN-235 are orally delivered investigational drugs that are designed to block biological pathways currently targeted by marketed injectable antibody drugs. Our orally stable peptide approach may offer a targeted therapeutic approach for GI and systemic compartments as needed. We believe that, compared to antibody drugs, these product candidates have the potential to provide improved safety due to minimal exposure in the blood, increased convenience and compliance due to oral delivery, and the opportunity for the earlier introduction of targeted oral therapy.

PN-943 is an investigational, orally delivered, gut-restricted α4β7 specific integrin antagonist for inflammatory bowel disease ("IBD"). We submitted a U.S. Investigational New Drug ("IND") application with the FDA for PN-943 in December 2019, which took effect in January 2020. During the second quarter of 2020 we initiated IDEAL, a 150 patient Phase 2 trial evaluating the safety, tolerability and efficacy of PN-943 in patients with moderate to severe UC. This trial includes a 12-week induction period and a 40-week open label extension. Patient enrollment in IDEAL was completed during the first quarter of 2022, and topline data from the study, including the 12-week induction period, is expected in the second quarter of 2022.

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 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.

In October 2020, we and Janssen announced the selection of two second-generation IL23-R antagonists for advancement into clinical development, PN-232 (JNJ-75105186) and PN-235 (JNJ-77242113). 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 favor of advancing PN-235, based on its superior potency and overall pharmacokinetic and pharmacodynamic profile. A PN-235 Phase 1 study was completed in Q4 2021. Janssen initiated FRONTIER 1, a Phase 2b clinical study of PN-235 in moderate-to-severe plaque psoriasis, in early 2022, and is expected to initiate a separate Phase 2 study of PN-235 in IBD in the second half of 2022**.**

During the fourth quarter of 2021, we received a $7.5 million milestone payment from Janssen triggered by the completion of data collection for PN-235 Phase 1 activities. We expect to earn a $25.0 million milestone in connection with the dosing of a third patient in the first Phase 2 study of a second-generation candidate, and a $10.0 million

milestone in connection with the dosing of a third patient in the second Phase 2 study of a second-generation candidate. We remain eligible for up to approximately $900.0 million in development-related milestone payments, in addition to the $87.5 million in milestones already received.

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.

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 HH, 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 2 ("JAK2") 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 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.

PV affects approximately 100,000 patients living in the United States, with a similar prevalence in Europe, representing an estimated market opportunity of approximately $1.0 billion to $2.0 billion. Approximately 14,000 new patients have been diagnosed with PV annually each year since 2017. 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. Although NCCN guidelines state that hematocrit levels should be maintained below 45% to reduce risk of cardiovascular and thrombotic events, less than 25% of patients in the large medical claims data set had all hematocrit test results under 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.

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. 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.

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.

To date we have received 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;
- The FDA granted Fast Track designation for rusfertide for the treatment of PV in December 2020; and
- The FDA granted Breakthrough Therapy Designation for rusfertide for the treatment of PV in June 2021.

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. Reenrollment continues with the target of 50 patients completing the full trial.

In December 2021, we presented two oral presentations and two posters relating to rusfertide at the American Society for Hematology's hybrid annual meeting, including updated interim Phase 2 results for the REVIVE and

PACIFIC studies for rusfertide in PV. These preliminary results as of September 2021 demonstrated dramatic decreases in the need for therapeutic phlebotomy in patients with PV, while maintaining control over blood hematocrit levels.

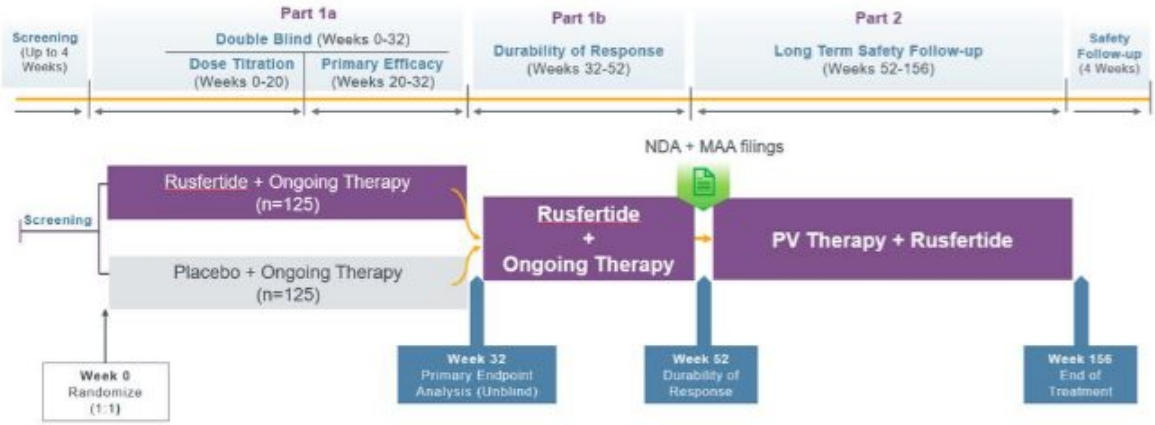
- We enrolled 63 patients in the ongoing REVIVE Phase 2 clinical trial of rusfertide in PV prior to the clinical hold and we are currently reenrolling approximately 20 additional patients to target approximately 50 patients enrolled through the end of a three-year open label extension. Of the 63 PV patients treated with rusfertide, the vast majority 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.

- Overall, rusfertide therapy resulted in rapid, sustained and durable hematocrit control without clinically meaningful changes in white blood cell and platelet counts. Subjects have been treated up to 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 myeloproliferative neoplasm blast phase which was deemed not to be related to rusfertide.

- Significant adverse events included syncope, peripheral artery aneurism, 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. All ISRs were transient, and no patient discontinued due to ISR.

- Results from the PACIFIC Phase 2 study in rusfertide for PV patients with high hematocrit levels presented at ASH 2021 demonstrated, post induction, weekly rusfertide treatment rapidly controlled hematocrit levels without the need for therapeutic phlebotomy.

Figure 2. VERIFY: Rusfertide Phase 3 PV Study Design



Based on ongoing end of REVIVE and PACIFIC Phase 2 trials feedback provided by the FDA's Division of Nonmalignant Hematology and written comments from the EMA, we expect to initiate screening in a global, randomized, double-blind placebo-controlled Phase 3 clinical trial of rusfertide in approximately 250 PV patients in the first quarter of 2022 (Figure 2).

Hereditary Hemochromatosis ("HH")

HH Overview and Market Opportunity

HH is an inherited blood disorder characterized by excessive absorption of iron due to a deficiency or dysregulation in hepcidin. Approximately one million people in the United States have high iron Fe (" HFE") gene mutations consistent with type 1 HFE-related hemochromatosis, the most common form of HH. Of these, 10 to 15 percent develop clinical manifestations of iron overload. Onset of clinical symptoms in HH patients typically occurs between ages 40 and 60, after significant iron accumulation. If left untreated, iron may accumulate in major organs such as the liver, pancreas, heart, and bones, which may lead to complications including diabetes, cardiomyopathy, and cirrhosis. To prevent the development of these associated complications, the goal of treatment in HH patients is to reduce the amount of iron in the body. Per American College of Gastroenterology guidelines, patients with elevated serum ferritin above 200 ng/mL in females and 300 ng/mL in males, along with transferrin saturation (TSAT) above 45%, will require treatment, most commonly phlebotomy. The initial phase of treatment with phlebotomy, called the induction phase, typically requires weekly phlebotomy until serum ferritin levels decrease to the target range of 50 to 100 ng/ml. Once serum ferritin has reached its goal level, HH patients transition to the maintenance phase of therapy, in which they typically require phlebotomy 3-4 times per year to maintain normal serum ferritin levels and prevent iron accumulation in the organs.

There is no approved medicine for the treatment of HH. Most HH patients who require treatment can be adequately managed with phlebotomy, which is effective in removing excess iron and preventing most of the complications associated with iron overload. There are small sub-populations of patients who require treatment for HH but who are intolerant or resistant to phlebotomy. HH patients who cannot be managed with phlebotomy are left at an increased risk of iron accumulation and associated complications, therefore, additional treatment options may be needed for these populations.

Clinical Development of Rusfertide in HH

In January 2020, we initiated a Phase 2 study of rusfertide in HH. This study was an open label, multicenter study designed to evaluate the effects of rusfertide in 16 adult patients over 24 weeks of treatment. Guidelines for HH focused on controlling baseline transferrin saturation ("TSAT") and ferritin to prevent long-term complications. Given the TSAT reductions from rusfertide observed to date in both healthy volunteers and beta-thalassemia and PV patients, as well as regulation of organ iron content in a mouse model of HH, we believe that a significant reduction in phlebotomy is possible with rusfertide. The endpoints of this POC study included change in TSAT and serum iron levels, reductions in phlebotomy requirements and an assessment of participant-reported outcomes.

We completed our Phase 2 POC study in HH during the fourth quarter of 2021. An abstract highlighting positive preliminary data our Phase 2 study of rusfertide in HH was orally presented at The Liver Meeting® 2021, hosted by the AASLD, which took place virtually in November 2021. In December 2021, we presented a poster on rusfertide in HH at the ASH 2021 Annual Meeting. These results from the Phase 2 study of rusfertide in HH demonstrated a significant reduction in the number of phlebotomies, lower serum iron and TSAT levels, and a reduction of liver iron content. Administration of rusfertide was generally well tolerated in patients with HH, with the most common adverse events being injection site reactions that were mild or moderate.

Based on the data described above, we are exploring clinical studies in HH sub-populations. Additional studies are required to further characterize the safety, efficacy and long-term outcomes in rusfertide for HH patients.

OVERVIEW OF INFLAMMATORY BOWEL DISEASE

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).

Market Overview

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.

Current Standard of Care in IBD

In recent years, treatment of IBD has evolved from a focus on successful symptom management to an emphasis on modifying the underlying disease to achieve long-term remission. While available treatments exist for moderate-to-severe IBD, there continues to be a significant medical need for novel, efficacious, safe and convenient treatments. New technologies and outcome measures have been developed to improve staging definitions and assessments of treatment benefit. Nonetheless, halting or reversing IBD progression has not yet been achieved with any single agent therapy, and attaining and maintaining long-term remission in most patients remains a significant unmet medical need.

Biosimilar infliximab and other tumor necrosis factor ("TNF") inhibitors are the first line standard of care in moderate-to-severe IBD. Anti-TNFs bind to and neutralize a central pro-inflammatory cytokine in the gut via systemic immunosuppression. As a result, they can be associated with infection and malignancy risk. Although the magnitude of these risks is relatively low, they are significant for the young IBD population who must continue on lifelong treatment. In addition, more than 10% of patients treated with anti-TNF agents lose response with each year of treatment. In 2014, a novel anti-trafficking mechanism launched with vedolizumab, marketed as Entyvio®, which blocks migration of leukocytes into the gut via α4β7 integrins. This mechanism remains the only true "gut selective" approach in the IBD market today, although formulation technologies can limit systemic exposure from orally delivered agents. Entyvio® has shown an excellent safety profile, although it requires intravenous administration. Entyvio® was followed by the launch of ustekinumab, marketed as Stelara®, in CD in 2016, which blocks inflammation produced through the IL-12 and IL-23 pathways, and tofacitinib, marketed as Xeljanz®, an orally delivered pan-Janus kinase ("JAK") inhibitor approved in UC.

A head-to-head trial called VARSITY comparing the long-term safety and efficacy of an anti-integrin and anti-TNFs has been completed. Entyvio® demonstrated superior rates of clinical remission and endoscopic improvement compared with Humira®, the market leader in the TNF inhibitor class. The first formal combination trials in IBD were

initiated in the last year, adding new mechanisms such as integrin inhibitors or IL-23 inhibitors to anti-TNFs. Most IBD experts now believe that combining treatment classes with additive or synergistic mechanisms of action will be required to attain the disease-modifying effects and lasting remissions in a larger group of patients documented in other areas of immunology, such as psoriasis or rheumatoid arthritis.

We believe 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 in order to prevent disease progression and irreversible gastrointestinal damage. Orally delivered peptide drugs PN-943 and PN-235 work on the same specific validated targets as FDA-approved injectable antibodies and have the potential to offer improved safety and compliance and to minimize the risk of immunogenicity associated with antibodies. We believe that these product candidates, if approved, have the potential to be used more broadly, including treatment of mild-to-moderate IBD.

Our IBD Solution: Orally Delivered Peptides as Targeted Therapies

For the IBD targets of interest, the size and nature of our peptides are carefully selected and modified so as to acquire the desired potency and specificity, and also to largely restrict their presence to the GI and systemic tissue compartments as needed when administered orally. These features translate to orally delivered, selective and potent peptide drug candidates with specific advantages compared to antibody drugs:

- *Oral administration*. We are developing our peptide therapeutics in a convenient capsule or tablet form intended for oral administration, particularly in combination with other oral therapies. We also believe oral administration may reduce many of the problems and limitations associated with injections or infusions, including injection site pain and local reactions, inconvenience, anxiety, high rates of immunogenicity and potential safety risks.

- *Potential for improved safety and tolerability compared to antibody drugs*.

    - *Oral and GI-restricted delivery minimizes systemic exposure in the blood.* Oral and GI-restricted delivery results in lower drug levels in the blood that may provide the potential for an enhanced safety profile over antibody drugs.

    - *Peptides can be cleared more quickly from systemic circulation.* Small molecules and peptides below a size threshold can be rapidly cleared from blood circulation by kidney filtration and excretion. Rapid clearance may be beneficial especially if patients need to discontinue therapy. In contrast, antibody drugs, because of their long plasma half-life, may take months to clear from blood circulation, leaving patients exposed to continued or increased safety risk.

    - *The likelihood of much lower immunogenicity of small stable peptides compared to antibody drugs reduces the risk of loss of response.* We believe that anti-drug antibodies are less likely to be elicited against constrained peptides, due to their small size, lack of epitope density, resistance to proteolysis, oral tolerance, and minimal systemic absorption.

- *Potential for localized delivery to site of disease.* We believe oral dosing of GI-restricted peptides results in substantially higher drug concentrations in the diseased GI tissue compartment compared to injectable antibody drugs. This targeted delivery to the site of action may lead to more immediate and significant target engagement at the site of active disease in the GI tissue compartment with the potential for improved efficacy.

In chronic GI diseases such as IBD, we believe that our orally delivered, peptide product candidates may offer improved delivery and the potential for improved safety and tolerability that may provide an overall benefit to patients, payors, and physicians.

PN-943: AN ORALLY DELIVERED α4β7 INTEGRIN ANTAGONIST

PN-943, a second-generation, orally delivered, gut-restricted α4β7 specific integrin antagonist, was discovered through our peptide technology platform and is being developed initially for patients with moderate-to-severe UC. A4β7 integrin is considered to be one of the most GI-specific biological targets for IBD due to its binding to MAdCAM-1, an extracellular protein that resides mostly in the GI vasculature. Like Entyvio®, which is dosed as an infusion and as an injectable antibody drug, PN-943 specifically inhibits α4β7 integrin. We have leveraged the development and regulatory path of Entyvio® and other approved antibody drugs for IBD to help inform the design of our clinical development studies.

Mechanism of Action and Rationale

Integrins, such as α4β7, are transmembrane proteins that regulate cellular movement into extravascular tissue and play an important role in modulating the inflammatory reaction in the gut. The α4β7 integrin is expressed on the surface of T cells, immune cells that help defend against foreign and potentially harmful substances that enter the body. The development of IBD is driven by the migration of α4β7 T cells into the GI tissue compartment and their subsequent activation within the GI tissue compartment. The entry of α4β7 T cells into the GI tissue compartment is facilitated by the protein-protein interactions between the α4β7 integrin and its corresponding ligand, MAdCAM-1, which is primarily expressed in the GI tissue compartment. Hence, the binding of α4β7 to MAdCAM-1 can be categorized as a GI-specific interaction and has been identified as an IBD-specific targeted therapeutic approach. By blocking the binding of α4β7 integrin to MAdCAM-1, PN-943 may prevent trafficking and activation of T cells, thereby reducing the inflammation that leads to the clinical manifestations and long-term implications of UC.

A4β7 for IBD is targeted by Entyvio®, which has demonstrated safety and efficacy in patients with moderate-to-severe UC and CD. Since PN-943 targets the same biological pathway as Entyvio®, we utilized similar PD-based POC in our pre-clinical studies and Phase 1 clinical trial to inform and guide our Phase 2 development program. We sourced these PD biomarker assays from public scientific publications and do not maintain any contractual arrangement providing access to this information with the makers of these marketed products.

PN-943 Pre-Clinical Proof-of-Concept Studies

We have completed extensive pre-clinical studies of PN-943 in which we established pharmacodynamic target engagement POC, including effects on receptor occupancy, T cell trafficking and mucosal healing in rodents and monkeys. Pre-clinical data indicated that PN-943 may be a more potent α4β7 integrin antagonist compound than PTG-100, our first-generation α4β7 inhibitor, without sacrificing its other positive attributes, such as selectivity and tolerability. PTG-100 shares the same α4β7 integrin target as Entyvio® for the treatment of moderate-to-severe UC and CD. We completed extensive pre-clinical studies of PTG-100 in which we established pharmacological POC and completed a Phase 1 clinical trial in Australia in 2016.

PN-943's Phase 1 Clinical Trial Overview

We completed a Phase 1 randomized, double-blind, placebo-controlled clinical trial of PN-943 in normal healthy male volunteers in Australia in 2019. The Phase 1 single ascending dose ("SAD") and multiple ascending dose ("MAD") components were conducted with a solution-based liquid formulation. In addition to determining the safety and tolerability and pharmacokinetics of PN-943, the SAD and MAD components of the trial evaluated PD-based POC through the assessment of α4β7 receptor occupancy and α4β7 target expression that indicate target engagement on peripheral blood memory T cells similar to what was done in the pre-clinical studies and in the Phase 1 trial with PTG-100. In the clinical trial, dose escalation proceeded from 100 mg up to 1,400 mg for the SAD portion and 1,000 mg for the MAD portion. The administration of PN-943 was well-tolerated in the Phase 1 study.

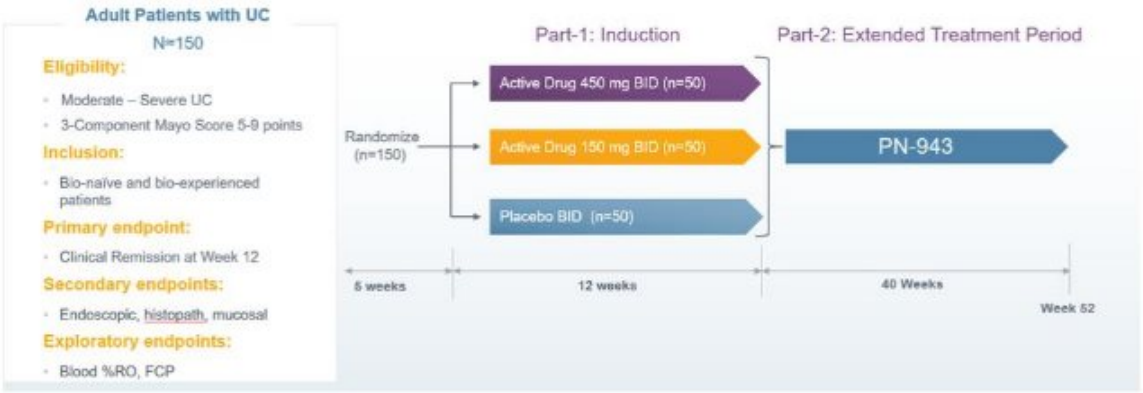
We reported results of the SAD part of the study during the second quarter of 2019 and the MAD part of the study during the third quarter of 2019. The pharmacodynamic results of target engagement were supportive of the three-fold higher potency of PN-943 as compared to PTG-100 and saturation at 1000 mg. This is consistent with data from pre-clinical studies and confirmed by this Phase 1 pharmacodynamic data. We believe this links PN-943 to greater

probability of success in a Phase 2 trial based on signs of clinical efficacy of PTG-100 in the Phase 2 PROPEL trial in UC patients.

PN-943 Phase 2 Clinical Trial Overview

We submitted a U.S. IND with the FDA for PN-943 in December 2019, which took effect in January 2020. During the second quarter of 2020, we initiated a global, randomized, double-blind placebo-controlled study called IDEAL evaluating the safety, tolerability and efficacy of PN-943 in approximately 150 patients with moderate-to-severe UC (Figure 3). Patient enrollment in IDEAL was completed during the first quarter of 2022, and topline data from the study, including the 12-week induction period, is expected in the second quarter of 2022.

Figure 3. IDEAL: PN-943 Phase 2 UC Study Design



PN-235: 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 "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.

In October 2020, we and Janssen announced the selection of two second-generation IL23-R antagonists for advancement into clinical development, PN-232 and PN-235. 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 PN-235, based on its superior potency and overall pharmacokinetic and pharmacodynamic profile. A PN-235 Phase 1 study was completed in Q4 2021. Janssen initiated FRONTIER 1, a Phase 2b clinical study of PN-235 in moderate-to-severe plaque psoriasis, in early 2022, and is expected to initiate a separate Phase 2 study of PN-235 in IBD in the second half of 2022**.** Janssen is primarily responsible for the conduct of all Phase 2 trials and we were primarily responsible for the conduct of the second-generation Phase 1 studies.

Mechanism of Action and Rationale

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 mucosal autocrine cascade that is an important pathway of many inflammatory diseases, including IBD. Furthermore, genetic analyses of IBD patients have implicated IL-23R mutations as a risk factor associated with susceptibility to IBD. The infused 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 IBD antibody drugs, such as guselkumab, target the p19 subunit of the IL-23 ligand and are specific inhibitors of the IL-23 pathway, which is believed to be an important driver of local IBD pathology. IL-12 is believed to be important in immune surveillance against the development of infections and malignancies.

We believe that our orally delivered IL-23R antagonist PN-235 may be a potent inhibitor of the IL-23 pathway for the treatment of IBD and non-IBD indications. By targeting IL-23R with PN-235, we believe PN-235 may restore proper immune function while minimizing the risk of systemic side effects. Several key cell types that reside in gut-associated lymphoid tissue ("GALT"), including T cells, innate lymphoid cells, and natural killer cells, increase their expression of IL-23R during the progression of IBD. Therefore, the high concentrations of PN-235 in GALT will facilitate access and binding to IL-23R expressed in the same tissue with the potential for concomitant efficacy benefits.

First-Generation IL-23R Antagonist PTG-200

PTG-200 was a first-generation investigational, orally delivered, IL-23R antagonist for the treatment of IBD. We completed a Phase 1 clinical trial of PTG-200 in Australia during the fourth quarter of 2018. The Phase 1 study was a randomized, double-blind, placebo-controlled, SAD and MAD-escalation trial in 80 normal healthy volunteers. The primary endpoint was safety and tolerability. Secondary endpoints included the identification of the maximally tolerated dose and the evaluation of pharmacokinetic parameters. Results of the Phase 1 study demonstrated that administration of PTG-200 was well-tolerated. No serious adverse events or dose-limiting toxicities were observed. The pharmacokinetic and pharmacodynamic parameters were consistent with the GI-restricted design of PTG-200.

Janssen submitted an IND for PTG-200 in CD during the second quarter of 2019, which took effect in July 2019. Janssen initiated a Phase 2 clinical study of PTG-200 in CD called PRISM in the fourth quarter of 2019. The global, randomized, double blind, placebo-controlled, Phase 2 study was designed to evaluate the efficacy of oral administration of PTG-200 in 90 patients with moderate-to-severe CD. This study was discontinued during the fourth quarter of 2021 in favor of focusing on the development of second-generation antagonists.

Second-Generation IL23-R Antagonist PN-235

PN-235, an orally delivered IL-23R specific antagonist for the treatment of IBD and non-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 hope to improve disease symptoms while potentially minimizing the risk of systemic side effects.

A Phase 1 study was initiated for PN-235 in December 2020. The Phase 1 for PN-235 study was designed to determine the safety, tolerability and pharmacokinetics of PN-235 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 PN-235 was well-tolerated. No serious adverse events or dose-limiting toxicities were observed. The pharmacokinetic and pharmacodynamic parameters of PN-235 were consistent with those predicted by preclinical studies. FRONTIER 1, a Phase 2b study in moderate-to-severe plaque psoriasis, was initiated in early 2022, and a Phase 2 study in IBD is expected to initiate in the second half of 2022. 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. Although the condition is not life-threatening, it is difficult to treat and response rates vary widely.

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 PN-943 and PN-235, 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 preclinical 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 PN-235, 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, HH 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.

Ruxolitinib, marketed as Jakafi®, was approved in 2014 for the treatment of adults with polycythemia vera 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 polycythemia vera, was approved with a black box warning in November 2021. Besremi is currently undergoing U.S. commercial launch with uncertain uptake at the present time.

There are currently no approved orally delivered peptide-based α4β7 or IL-23R products for IBD. Our principal competition with similar mechanisms of action in the treatment of IBD will come from companies with injectable agents in the anti-integrin class and the anti-IL-23 class that are or will be approved by 2028, including:

- Takeda's vedolizumab (Entyvio®) IV and SC;
- Abbvie's risankizumab (Skyrizi®) SC (UC and CD Phase 3)
- Janssen's guselkumab (Tremfya®) SC (UC and CD); and
- 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; next-generation selective JAK1/3 inhibitors, including Abbvie's upadacitinib (Rinvoq®) (UC and CD) and Pfizer's abrocitinib (Cibinqo®) (UC); 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. Anti-IL-23 antibodies are also demonstrating positive data in IBD. Many other agents are in early- stage development in IBD, including injectable anti-TLIA antibodies by Pfizer and Prometheus.

COVID-19 Business Update

We are continuing to closely monitor the impact of the ongoing global COVID-19 pandemic on our business and have taken and continue to take proactive efforts designed to protect the health and safety of our patients, study investigators, clinical research staff and employees, and to maintain business continuity. Our laboratory facilities are open for research activities with heightened safety measures designed to minimize occupational exposure and reduce transmission of COVID-19 within our workplace. Our non-laboratory employees telecommute at least part-time. We have experienced relatively minor impacts on productivity overall, which were experienced primarily in as our personnel adjusted to working remotely in the early stages of the COVID-19 pandemic. Enrollment in certain of our clinical studies has been adversely affected by the pandemic. It is possible the pandemic will have a more significant negative impact on our business in the future, depending on the depth of the effects and the duration of the crisis, including the development and spread of COVID-19 variants. We cannot predict whether these trends will continue or be exacerbated. For information regarding the current and potential impacts of the effects of the COVID-19 pandemic on our business, see Item 1A Risk Factors and Part II, Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations—Overview" elsewhere in this Form 10-K.

Material Agreements

Janssen License and Collaboration Agreement

On July 27, 2021, we entered into an amended and restated License and Collaboration Agreement ("Restated Agreement") with Janssen. The Restated Agreement amends and restates the License and Collaboration Agreement, dated May 26, 2017, by and between us and Janssen (as amended by the First Amendment thereto, effective May 7, 2019, the "Original Agreement"). 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. The Original Agreement became effective on July 13, 2017. 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. See "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 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 "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 needed quantities of 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. 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, among other things, 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 before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold. In such a 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, which include the requirement that all research subjects provide their informed consent in writing before their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, 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 submission ex-US). In addition, an IRB or ethics committee ("EC") must review and approve the plan for any clinical trial at each institution participating in the clinical trial before it commences at that site. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health ("NIH") for public dissemination on their www.clinicaltrials.gov website.

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 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, 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, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, 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. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. 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

Assuming 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 things, 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 a substantial application user fee. Under the Prescription Drug User Fee Act ("PDUFA") guidelines that are currently in effect, the FDA has a goal 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 because the FDA has approximately two months to make a "filing" decision.

In addition, under the Pediatric Research Equity Act of 2003 ("PREA"), as amended and reauthorized, 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. The REMS plan could 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 additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, 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, in some cases, 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 in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately 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, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which 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 changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Fast Track Designation

The FDA has various programs, including fast track designation, which are intended to expedite or simplify the process for the development and FDA review of drugs that are intended 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 earlier than under standard FDA review procedures. Under the fast track program, the sponsor of a new drug candidate may request that the FDA designate the drug candidate for a specific indication as a fast track drug concurrent with, or after, the filing of the IND for the drug candidate. 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. The FDA will determine that 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 factors. 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 period 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.

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.

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, or if it 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 as 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.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, 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 prior 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 and are subject to periodic unannounced inspections by the FDA and these 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 also require investigation and correction of any deviations from cGMP requirements and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. 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 events of unanticipated severity or frequency, or 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, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending 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 actively 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/or 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. The coverage determination process 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 if administrative burdens make our products less desirable to use.

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, results of operations and financial condition.

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, among other things, 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 or constrain 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 requirements mandated by the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. 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 certain individuals who fail to 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, effective January 1, 2021, also eliminated the health insurance tax. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, 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. 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. Such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, 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 used several means to propose or implement drug pricing reform, including 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 has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers.

On November 20, 2020, the Centers for Medicare & Medicaid Services ("CMS") issued an interim final rule implementing President Trump's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule, and in August 2021, the Biden administration issued an interim rule that would rescind the most favored nation drug pricing rule. At the state level, 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, particularly in light of the new presidential administration, 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 foreign, federal, state, or private payors for health care treatment and services may take in response to any 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 government and the states 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, but are not limited to, 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 federal health care programs' Anti-Kickback Statute, which prohibits, among other things, 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, among other things, 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 physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, and ownership and investment interests held by physicians and their immediate family members and, beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified nurse anesthetists and certified nurse-midwives.

The majority of states also have statutes or regulations similar to the aforementioned 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 or our operations 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, among other things, clinical studies and any commercial sales and distribution of our products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission and approval of a clinical trial application much like the IND but specific to a clinical trial prior to the commencement of the human clinical study.

The requirements and process governing the conduct of clinical studies, the protection of personal data, product licensing, pricing and reimbursement vary from country to country. If we fail to comply with applicable foreign

regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Human Capital

As of December 31, 2021, we had 118 full-time equivalent employees, 92 of whom were in research and development, of which four hold an M.D. and 23 hold Ph.D. degrees. The remaining 26 employees worked in finance, legal, business development, human resources and administrative support, of which one holds a Ph.D. 104 of our full-time equivalent employees are located in the United States and 14 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, 2021, nearly 65% of our workforce identify as members of underrepresented ethnic communities and 51% 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 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 principal executive offices are located at 7707 Gateway Boulevard, Suite 140, Newark, California 94560. Our telephone number is (510) 474-0170. 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"). We also show detail about stock trading by corporate insiders by providing access to SEC Forms 3, 4

and 5. This information may also be obtained from the SEC's on-line database, which is located at www.sec.gov. Our common stock is traded on The Nasdaq Stock Market, LLC under the symbol "PTGX."

Prior to December 31, 2021, we were an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012. As such, we were eligible for exemptions from various reporting requirements applicable to other public companies that are not emerging growth companies, including, but not limited to, not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002 and reduced disclosure obligations regarding executive compensation. As of December 31, 2021, we are no longer an emerging growth company and are no longer exempt from such reporting requirements.

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 the COVID-19 Pandemic

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

The extent to which the ongoing 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. The effectiveness of actions taken in the United States and other countries to contain, ameliorate the impact of and treat the disease and to address its impact, is not yet known. A number of jurisdictions, including California and other jurisdictions in the United States, have at various times begun re-opening only to return to restrictions in the face of increases in new COVID-19 cases. As the COVID-19 pandemic continues, 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;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of clinical trials;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others or interruption of clinical trial subject visits and study procedures, which may impact the integrity of subject data and clinical study endpoints;
- limitations in resources, including our employees, that would otherwise be focused on the conduct of our business or our current or planned clinical trials or preclinical research, including because of sickness, the desire to avoid contact with large groups of people or restrictions on movement or access to our facility as a result of government-imposed "shelter-in-place" or similar working restrictions;
- interruptions or delays in the operations of the U.S. Food and Drug Administration ("FDA") or other regulatory authorities, which may impact review and approval timelines;
- delays in manufacturing, receiving the supplies, materials and services needed to conduct clinical trials and preclinical research;
- changes in regulations as part of a response to the COVID-19 pandemic which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs or require us to discontinue the clinical trial altogether; and
- delays in necessary interactions with regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or furloughs of government or contractor personnel.

In addition, since March 2020, Alameda County, California, where our headquarters are located, has been subject to various "shelter-in-place" regulations and guidance related to the pandemic. While the "shelter-in-place" orders have terminated or been phased out along with the reopening of businesses in Alameda County, California, we may continue to be subject to capacity restrictions and health and safety recommendations that encourage continued social distancing and remote work, limiting or ability to return to pre-pandemic levels of activity. Our laboratory facilities currently remain open with heightened safety measures designed to minimize occupational exposure and reduce transmission of COVID-19 within our workplace. Our non-laboratory employees telecommute at least part-time, which may impact certain of our operations over the near term and long term. In addition, we may in the future resume a more restrictive remote work model due to the pandemic. These disruptions in our operations could negatively impact our business, operating results and financial condition.

Further, we may be required to develop and implement additional clinical study policies and procedures designed to help protect study participants from the COVID-19 virus and its variants, which may include using telemedicine visits, remote monitoring of patients and clinical sites, shipping drug product directly to patients rather than clinical sites, and measures to ensure that clinical data are collected pursuant to the study protocol and consistent with good clinical practices ("GCPs"). Patients who miss scheduled appointments, any interruption in study drug supply, or other consequence that may result in incomplete data being generated during a study as a result of the pandemic must be adequately documented and justified in accordance with FDA guidance. These additional requirements may be difficult to fulfill and may result in an incomplete data set, which could negatively impact the study results.

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.

Risks Related to Clinical Development

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

We are a biopharmaceutical company with a 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 Phase 1 and Phase 2 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 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 in registrational or pivotal clinical trials or 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 U.S. Food and Drug Administration ("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 conduct larger, more 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, for rusfertide for 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. 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, the announcement of the premature discontinuation of the global Phase 2 clinical trial of PTG-100 for the treatment of moderate-to-severe ulcerative colitis ("UC") in March 2018 due to the interim analysis meeting futility criteria on the primary endpoint of clinical remission (that was subsequently confirmed to be due to human error in endoscopy reads by the original vendor) significantly depressed our stock price. Our stock price also dropped significantly following the announcement in September 2021 of a full clinical hold imposed by the FDA on our rusfertide clinical studies related to a non-clinical finding in a rasH2 transgenic mouse study, and experienced volatility following the removal of the hold in October 2021.

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 expect to have 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 never conducted a Phase 3 clinical trial or submitted an NDA. As a result, we have no history or track record to rely on when entering 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. Clinical trials can be delayed for a variety of reasons, including if a clinical trial is modified, suspended or terminated by us, 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, on September 16, 2021, a full clinical hold by the FDA for the rusfertide clinical studies was triggered by a non-clinical finding in a 26-week rasH2 transgenic mouse model indicating benign and malignant subcutaneous skin tumors. On October 8, 2021, the FDA removed the full clinical hold on our rusfertide clinical studies and dosing in all clinical studies of rusfertide could be resumed. For additional information, see the Risk Factor – "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 inflammatory bowel disease and in hematologic disorders that are currently ongoing, especially in Phases 2 and 3, making it highly competitive and challenging to recruit subjects. Furthermore, any negative results we may report in clinical trials of our product candidates, such as the premature termination of our Phase 2 clinical trial of PTG-100 for the treatment of moderate-to-severe UC, may make it difficult or impossible to recruit and retain patients in other 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. For example, a limited number of subjects are enrolled in our PN-943 Phase 2 IDEAL study at clinical sites in Ukraine and Russia. While we do not expect the ongoing conflict between Ukraine and Russia to delay our topline data announcement for the trial in the second quarter of 2022, the impact of the conflict on those subjects is uncertain at this time.

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, since our product candidate PN-943 and PN-235, the product candidate under development in our collaboration with Janssen, 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 the Company's clinical studies for rusfertide were placed on a full clinical hold by the FDA. On October 8, 2021, per the FDA, the full clinical hold was lifted and dosing in all clinical studies of rusfertide could be resumed. 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. We are working closely with study investigators and clinical trial sites to resume dosing of patients in ongoing clinical trials with rusfertide after patients have been reconsented. The clinical hold was initially triggered by a recent 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. No additional cancer cases, and no other unexpected safety signals, surfaced in this process.

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 focused on research programs and product candidates mainly on the development of rusfertide, PN-943 and the product candidates subject to our Janssen collaboration. 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, 2021, we had an accumulated deficit of $409.4 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 at least several years, if ever, and we do not yet have any product candidates in registration or pivotal clinical trials. 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 our Janssen License and Collaboration Agreement is terminated, we may not receive any additional fees or milestone payments under that agreement. Absent the funding support from this

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, 2021, we had cash, cash equivalents and marketable securities of $326.9 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, 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 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 PN-235, our business and business prospects would be adversely affected.

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 Janssen License and Collaboration Agreement, 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 PN-235 and any other second-generation compounds. Janssen's decisions with respect to such development will affect the timing and availability of potential future payments under the agreement, if any. 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 PTG-200, and further development of PN-232 was also discontinued during the quarter, both in favor of PN-235, a novel peptide with exceptional, low picomolar potency and with superior in vivo stability. If the Janssen License and Collaboration Agreement 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 PN-235 or other matters under the Janssen License and Collaboration Agreement, such as interpretation of the agreement or ownership of proprietary rights. Also, after the period of collaborative development ends under the agreement, Janssen will have 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 Janssen License and Collaboration Agreement, 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 collaboration. 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 European Medicines Agency ("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, 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 ongoing COVID-19 pandemic or otherwise, we could experience delays, disruptions, suspensions or termination of our clinical study 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 EU 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 European Union ("EU"). 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 Janssen License and Collaboration Agreement, 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.

For example, in the United States in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, (collectively, the "ACA") was enacted to increase access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for health care and the health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The law has continued the downward pressure on pharmaceutical pricing, especially under the Medicare program, and increased the industry's regulatory burdens and operating costs.

There have been executive, judicial and Congressional challenges to certain aspects of the ACA. For example, former President Trump signed Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. 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 (the "Tax Act") included a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to 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, effective January 1, 2021, also eliminated the health insurance tax. Further, the Bipartisan Budget Act of 2018 (the "BBA") among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." On December 14, 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Act. Additionally, on December 18, 2019, the U.S. Court of Appeals for the 5th Circuit upheld the District Court ruling that the individual mandate was unconstitutional and remanded the case back to the District Court to determine whether the remaining provisions of the ACA are invalid as well. The U.S. Supreme Court is currently reviewing this case, but it is unclear when a decision will be made. On February 10, 2021, the Biden administration withdrew the federal government's support for overturning the ACA. Although the U.S. Supreme Court has not yet ruled on the constitutionality of the ACA, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace, which began on February 15, 2021 and will remain open until August 15, 2021. The executive order also instructs certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how the Supreme Court ruling, other such litigation and the healthcare reform measures of the Biden administration will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. These changes included aggregate reductions to Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2030 unless additional action is taken by Congress. COVID-19 relief legislation suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2021. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers and increased the statute of limitations period in which the government may recover overpayments to providers from three to five years.

Heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products has resulted in several recent Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. 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 has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed until January 1, 2023. On November 20, 2020, the Centers for Medicare & Medicaid Services ("CMS") issued an interim final rule implementing President Trump's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. On December 28, 2020, the United States District Court in Northern California issued a nationwide preliminary injunction against implementation of the interim final rule. At the state level, 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. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product candidates, if approved.

We expect that additional state and federal healthcare reform measures will be adopted in the future, particularly in light of the new presidential administration, any of which could limit the amounts that federal and state governments will pay for healthcare therapies, which could result in reduced demand for our product candidates or additional pricing pressures. Further, it is possible that additional governmental action is taken in response to the COVID-19 pandemic.

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.

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 preclinical 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 preclinical 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 June 2020, the FDA accepted 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. The FDA approved this application in November 2021. 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 PV and hereditary hemochromatosis ("HH") 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.

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 Janssen License and Collaboration Agreement, 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. 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, and we may experience difficulties in managing this growth.

As of December 31, 2021, we had 118 full-time equivalent employees, including 92 full-time equivalent employees engaged in research and development. 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, 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 European Union, 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. patents covering PN-943 and PTG-200 expire in 2035, and our granted U.S. patent covering rusfertide expires in 2034. 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 IL-23R, α4β7 integrin or hepcidin mimetics, 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 Janssen License and Collaboration 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.

Our stock price has fluctuated in the past and is likely to be volatile in the future. From January 1, 2019 through December 31, 2021, the reported sale price of our common stock has fluctuated between $4.47 and $50.54 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.

Volatility in our share price could subject us to securities class action litigation.

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 obligated 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. Our public float on June 30, 2021 was greater than $700.0 million, and our independent registered public accounting firm is required to attest to the effectiveness of our internal control over financial reporting beginning with this Annual Report for the fiscal year ending December 31, 2021. If we have a material weakness, we would receive an adverse opinion regarding our internal control over financial reporting from our independent registered accounting firm.

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 and in the current year, 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 business needs for at least the next 12 months and 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 aware of any pending or threatened legal proceeding against us that we believe could have a material adverse effect on our business, operating results or financial condition. We were a party in the arbitration proceeding that was resolved during the third quarter of 2021 described in Note 11 to the Consolidated Financial Statements elsewhere in this Annual Report on Form 10-K.

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." Prior to August 11, 2016, there was no public market for our common stock.

Stockholders

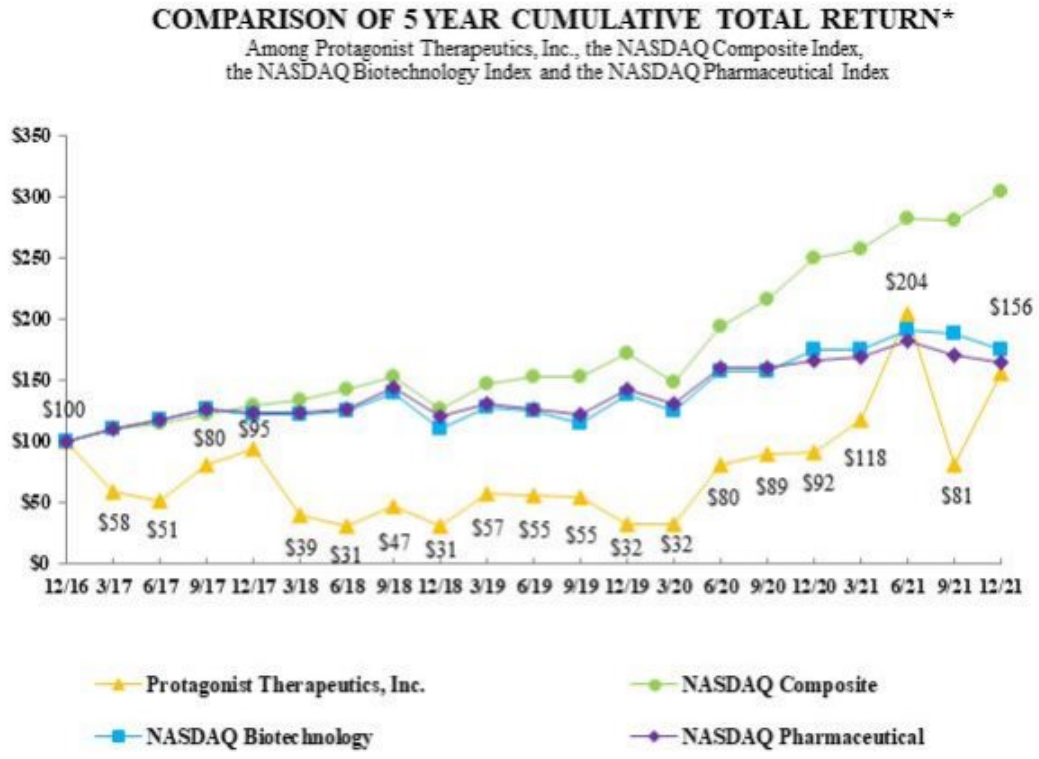
As of the close of business on February 15, 2022, there were two stockholders of record of our common stock. The number of stockholders of record is based upon the actual number of stockholders registered at such date and does not include holders of shares in "street names" or persons, partnerships, 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 is not to be incorporated by reference into any filing we make under 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 the investment on the date specified in each of our common stock, the Nasdaq Composite Index, the Nasdaq Biotechnology Index, and the Nasdaq Pharmaceutical Index. The graph tracks the performance of a $100 investment in our common stock and in each index (with the reinvestment of all dividends) from December 31, 2016 to December 31, 2021.



The stock price performance included in the graph is not necessarily indicative of future stock performance.

Sale of Unregistered Securities

None.

Repurchases of Shares or of Company 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 multiple peptide-based new chemical entities in different stages of development, all derived from the Company's proprietary technology platform. Our clinical programs address two broad categories of diseases; (i) hematology and blood disorders, and (ii) inflammatory and immunomodulatory diseases.

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. 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. We initiated REVIVE, a Phase 2 proof of concept ("POC") study in the blood disorder polycythemia vera ("PV"), in the third quarter of 2019. We initiated a Phase 2 POC study in hereditary hemochromatosis ("HH") in January 2020, which was completed during the fourth quarter of 2021. During the first quarter of 2021, we initiated PACIFIC, another Phase 2 study for rusfertide in up to 20 patients diagnosed with PV and with routinely elevated hematocrit levels (>48%).

In June 2021, we presented updated Phase 2 data supporting the long-term efficacy of rusfertide in PV during an oral presentation at the European Hematology Association ("EHA") 2021 Virtual Congress. An abstract highlighting positive preliminary data from our Phase 2 study of rusfertide in HH was orally presented at The Liver Meeting® 2021, hosted by the American Association for the Study of Liver Diseases ("AASLD"), which took place virtually in November 2021. In December 2021, two abstracts highlighting positive updated data from our REVIVE and PACIFIC Phase 2 studies of rusfertide in PV were orally presented at the American Society of Hematology ("ASH") 2021 Annual Meeting, in addition to three poster presentations on rusfertide in PV and HH. These results 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 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.

On September 16, 2021, the FDA placed a clinical hold on our rusfertide clinical studies 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 clinical study protocols of 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.

We enrolled 63 patients in the ongoing REVIVE Phase 2 clinical trial of rusfertide in PV prior to the clinical hold, and we are currently enrolling approximately 20 patients to target approximately 50 patients enrolled through the end of a three-year open label extension. Based on ongoing end of Phase 2 feedback provided by the FDA's Division of Nonmalignant Hematology and written comments from the European Medicines Agency ("EMA"), we expect to initiate VERIFY, a global Phase 3 clinical trial of rusfertide in PV in the first quarter of 2022. Patient enrollment into VERIFY is expected to be completed in the first half of 2023. In addition, we completed our Phase 2 POC study in HH, our second indication, during the fourth quarter of 2021.

To date we have received 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;
- The FDA granted Fast Track designation for rusfertide for the treatment of PV in December 2020; and
- The FDA granted Breakthrough Therapy Designation for rusfertide for the treatment of PV in June 2021.

Our alpha-4-beta-7 ("α4β7") antagonist PN-943 and our Interleukin-23 receptor ("IL-23R") antagonist compound PN-235 are orally delivered investigational drugs that are designed to block biological pathways currently targeted by marketed injectable antibody drugs. Our orally stable peptide approach may offer a targeted therapeutic approach for GI and systemic compartments as needed. We believe that, compared to antibody drugs, these product candidates have the potential to provide improved safety due to minimal exposure in the blood, increased convenience and compliance due to oral delivery, and the opportunity for the earlier introduction of targeted oral therapy.

PN-943 is an investigational, orally delivered, gut-restricted α4β7 specific integrin antagonist for inflammatory bowel disease ("IBD"). We submitted a U.S. Investigational New Drug application with the FDA for PN-943 in December 2019, which took effect in January 2020. During the second quarter of 2020 we initiated IDEAL, a 150 patient Phase 2 trial evaluating the safety, tolerability and efficacy of PN-943 in patients with moderate to severe UC. This trial includes a 12-week induction period and a 40-week open label extension. Patient enrollment in IDEAL was completed during the first quarter of 2022, and topline data from the study, including the 12-week induction period, is expected in the second quarter of 2022.

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 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.

In October 2020, we and Janssen announced the selection of two second-generation IL23-R antagonists for advancement into clinical development, PN-232 (JNJ-75105186) and PN-235 (JNJ-77242113). 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 favor of advancing PN-235, based on its superior potency and overall pharmacokinetic and pharmacodynamic profile. A PN-235 Phase 1 study was completed in Q4 2021. Janssen initiated FRONTIER 1, a Phase 2b clinical study of PN-235 in moderate-to-severe plaque psoriasis, in early 2022, and is expected to initiate a separate Phase 2 study of PN-235 in IBD in the second half of 2022**.**

During the fourth quarter of 2021, we received a $7.5 million milestone payment from Janssen triggered by the completion of data collection for PN-235 Phase 1 activities. We expect to earn a $25.0 million milestone in connection with the dosing of a third patient in the first Phase 2 study of a second-generation candidate, and a $10.0 million milestone in connection with the dosing of a third patient in the second Phase 2 study of a second-generation candidate. We remain eligible for up to approximately $900.0 million in development-related milestone payments, in addition to the $87.5 million in milestones already received.

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.

COVID-19 Business Impact

We are subject to risks and uncertainties as a result of the ongoing COVID-19 pandemic. We are continuing to closely monitor the impact of the COVID-19 pandemic on our business and have taken and continue to take proactive efforts to protect the health and safety of our patients, study investigators, clinical research staff and employees, and to maintain business continuity. The extent of the impact of the COVID-19 pandemic on our activities is highly uncertain and difficult to predict, as the response to the pandemic is ongoing and information continues to evolve. Capital markets and economies worldwide have been significantly impacted by the COVID-19 pandemic and may be further impacted in the future. Such economic disruption could have a material adverse effect on our business. Policymakers around the globe have responded with fiscal policy actions to support the healthcare industry and economy as a whole. The magnitude and overall effectiveness of these actions remains uncertain.

The severity of the impact of the COVID-19 pandemic on our activities will depend on a number of factors, including, but not limited to, the duration and severity of the pandemic, including the severity of any additional periods of increases or spikes in the number of cases in the areas we, our suppliers and our manufacturers operate and areas where our clinical trial sites are located; the development and spread of COVID-19 variants; the timing, extent, effectiveness and durability of COVID-19 vaccine programs or other treatments; and new or continuing travel and other restrictions and public health measures, such as social distancing, business closures or disruptions. Accordingly, the extent and severity of the impact on our existing and planned clinical trials, manufacturing, collaboration activities and operations is uncertain and cannot be fully predicted. 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 and collaboration activities, continued difficulty in recruiting patients for these clinical trials, delays in manufacturing and collaboration activities, supply chain disruptions, the ongoing impact on our operating activities and employees, and the ongoing impact of any initiatives or programs that we may undertake to address financial and operational challenges. As of the date of issuance of this Annual Report on Form 10-K, the extent to which the COVID-19 pandemic may materially impact our future financial condition, liquidity or results of operations is uncertain.

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 $125.6 million, $66.2 million and $77.2 million for the years ended December 31, 2021, 2020 and 2019, respectively. As of December 31, 2021, we had an accumulated deficit of $409.4 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, development 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 an amended and restated License and Collaboration Agreement ("Restated Agreement") with Janssen. The Restated Agreement amends and restates the License and Collaboration Agreement, dated May 26, 2017, by and between us and Janssen (as amended by the First Amendment thereto, effective May 7, 2019, the "Original Agreement"). 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. The Original Agreement became effective on July 13, 2017. 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. 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. In the fourth quarter of 2021, we received a $7.5 million milestone payment from Janssen triggered by data collection activities for the first Phase 1 clinical trial of a second-generation compound during the fourth quarter of 2021. 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 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, 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

Due to the ongoing COVID-19 pandemic, there has been uncertainty and disruption in the global economy and financial markets. We have taken into consideration any known COVD-19 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 issuance 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, it 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, and 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).

The period between when we transfer control of promised goods or services and when we receive payment is expected to be one year or less, which is consistent with our historical experience. Upfront payment contract liabilities resulting from our license and collaboration agreements do not represent a financing component as the payment is not financing the transfer of goods and services, and the technology underlying the licenses granted reflects research and development expenses already incurred by us. As such, we do not adjust our revenues for the effects of a significant financing component.

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 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. We accrue 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. 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 number and location of sites activated may vary from our estimates, resulting in adjustments to expense 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 funds from grants under government programs as a reduction of research and development expenses when the related research costs are incurred. In addition, we recognize the funds 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 allocate direct costs 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; 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.

The following table summarizes our research and development expenses incurred during the periods indicated:

	Year Ended December 31,		
	2021	2020	2019
Clinical and development expense — rusfertide (PTG-300)	$ 55,382	$ 32,395	$ 30,325
Clinical and development expense — PN-943	37,655	23,354	20,924
Clinical and development expense — PN-235	4,777	317	—
Clinical and development expense — PN-232	2,037	—	—
Clinical and development expense — PTG-200	23	925	9,414
Clinical and development expense — PTG-100	374	540	288
Preclinical and drug discovery research expense	24,943	18,453	4,162
Milestone payment obligation to former collaboration partner	4,000	—	—
Grants and tax incentives expense reimbursement, net	(3,185)	(1,478)	(110)
Total research and development expenses	$ 126,006	$ 74,506	$ 65,003

We expect our research and development expenses will increase as we progress our product candidates into later stage clinical trials, add to the number of ongoing clinical trials, advance our discovery research projects into the pre-clinical stage, continue our early-stage research and prepare for the commercialization of our product candidates. 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.

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 supplies. We expect to continue to incur expenses to support our continued operations as a public company, including expenses related to existing and future compliance with rules and regulations of the SEC and those of the national securities exchange on which our securities are traded, insurance expenses, investor relations, 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

Comparison of the Year ended December 31, 2021 and 2020

	Year Ended December 31,		Dollar Change	% Change
	2021	2020		
	(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 following the amendment of our collaboration agreement for the development of IL-23R assets with Janssen. This cumulative catch-up was primarily the result of an acceleration of our cumulative performance completed under our obligation, following the amendment to the collaboration which reduced the remaining services that we are responsible to provide. Revenue for the year ended December 31, 2020 included an update in the amounts forecast 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, coupled with continued performance and delivery of services under the Janssen License and Collaboration Agreement.

We have determined that the transaction price of the initial performance obligation under the Restated Janssen License and Collaboration 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 includes $87.5 million of nonrefundable payments received to date, $17.9 million of reimbursement from Janssen for services performed for IL-23R antagonist compound research costs and other services and estimated variable consideration consisting of $8.2 million of development cost reimbursement receivable 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 the Company under the agreement and the Company's remaining shared development costs following the Second Amendment to the Janssen License and Collaboration Agreement. We re-evaluate the transaction price each reporting period and as uncertain events are resolved or other changes in circumstances occur.

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 — PN-235	4,777	317	4,460	1,407
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)
Preclinical and 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; $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; $4.5 million of clinical trial and development costs for the Phase 1 PN-235 initiated in December 2020; $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 $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 at 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 increase 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 recent record low interest rate environment 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 as of 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 differs from our federal statutory rate of 21% primarily because our losses cannot 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 is necessary for our Australia subsidiary. Income tax expense for 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. We maintained a full valuation allowance on our tax position as of December 31, 2021.

Comparison of the Years ended December 31, 2020 and 2019

	Year Ended December 31, 2020	2019	Dollar Change	% Change
	(Dollars in thousands)			
License and collaboration revenue - related party	$ 28,628	$ 231	$ 28,397	*
Operating expenses:				
Research and development [1]	74,506	65,003	9,503	15
General and administrative [2]	18,638	15,749	2,889	18
Total operating expenses	93,144	80,752	12,392	15
Loss from operations	(64,516)	(80,521)	16,005	(20)
Interest income	900	2,813	(1,913)	(68)
Interest expense	(598)	(169)	(429)	254
Loss on early repayment of debt	(585)	—	(585)	*
Other expense, net	(46)	(1)	(45)	*
Loss before income tax (expense) benefit	(64,845)	(77,878)	13,033	(17)
Income tax (expense) benefit	(1,305)	691	(1,996)	(289)
Net loss	$ (66,150)	$ (77,187)	$ 11,037	(14)

[1] Includes $4.1 million and $4.4 million of non-cash stock-based compensation expense for the years ended December 31, 2020 and 2019, respectively.

[2] Includes $3.8 million and $4.0 million of non-cash stock-based compensation expense for the years ended December 31, 2020 and 2019, respectively.

*Percentage not meaningful

License and Collaboration Revenue

License and collaboration revenue increased $28.4 million from $0.2 million for the year ended December 31, 2019 to $28.6 million for the year ended December 31, 2020. The increase in license and collaboration revenue was primarily due to an update in the amounts forecast for future services remaining to be performed under the Janssen License and Collaboration Agreement, correspondingly increasing our overall cumulative percentage of completion of our performance obligation during year ended December 31, 2020, coupled with continued performance and delivery of services under the ongoing Janssen License and Collaboration Agreement. The increase in license and collaboration revenue for the year ended December 31, 2020 also included the impact of a one-time cumulative adjustment related to the application of revenue recognition principles following the May 2019 amendment of the Janssen License and Collaboration Agreement that reduced 2019 revenue by $9.4 million. The contract modification resulted in an increase in the transaction price and additional deliverables under the initial performance obligation, leading to an overall corresponding decrease in the cumulative percentage of completion of our performance obligation for the Janssen License and Collaboration Agreement during the second quarter of 2019.

We determined that the transaction price of the Janssen License and Collaboration Agreement was $98.6 million as of December 31, 2020, a decrease of $14.3 million from the transaction price of $112.9 million at December 31, 2019. 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 includes the $50.0 million upfront payment, the $25.0 million payment received upon the effectiveness of the First Amendment, the $5.0 million payment triggered by the successful nomination of a second-generation compound, $17.9 million of reimbursement from Janssen for services performed for PTG-200 Phase 2 and for second-generation compound research costs and other services, and estimated variable consideration consisting of a $7.5 million milestone payment subject to the completion of a Phase 1 study for a second-generation compound, offset by $6.8 million of net cost reimbursement to Janssen for services performed. The decrease in transaction price from December 31, 2019 to December 31, 2020 was due primarily to a decrease in the forecast of remaining services to be provided under the initial performance obligation. We re-evaluate the transaction price each reporting period and as uncertain events are resolved or other changes in circumstances occur.

Research and Development Expenses

	Year Ended December 31,		Dollar	%
	2020	2019	Change	Change
	(Dollars in thousands)			
Clinical and development expense — rusfertide (PTG-300)	$ 32,395	$ 30,325	$ 2,070	7
Clinical and development expense — PN-943	23,354	20,924	2,430	12
Clinical and development expense — PN-235	317	—	317	*
Clinical and development expense — PTG-200	925	9,414	(8,489)	(90)
Clinical and development expense — PTG-100	540	288	252	88
Preclinical and drug discovery research expense	18,453	4,162	14,291	343
Grants and tax incentives expense reimbursement, net	(1,478)	(110)	(1,368)	*
Total research and development expenses	$ 74,506	$ 65,003	$ 9,503	15

*Percentage not meaningful

Research and development expenses increased $9.5 million, or 15%, from $65.0 million for the year ended December 31, 2019 to $74.5 million for the year ended December 31, 2020. The increase included a $14.3 million increase in pre-clinical and discovery research expenses, including pre-clinical costs related to our second-generation research collaboration efforts with Janssen, a $2.4 million increase in PN-943 clinical trial and development expenses following the initiation of the Phase 2 trial in UC in 2020, a $2.1 million increase in rusfertide clinical trial and development expenses, including the ongoing Phase 2 trials in PV and HH, and $0.3 million of Phase 1 clinical trial and development expenses for PN-235. These increases were partially offset by a decrease of $8.5 million for PTG-200 clinical trial and development expenses under the Janssen License and Collaboration Agreement due to timing of deliverables and related cost sharing arrangements, and the impact of a $1.3 million reversal of previously recorded reductions to research and development expenses in connection with the tax incentive from Australia in 2019. Research and development expenses for the year ended December 31, 2020 included increased personnel costs due to an increase in research and development headcount from 54 full-time equivalent employees at December 31, 2019 to 59 full-time equivalent employees at December 31, 2020.

General and Administrative Expenses

General and administrative expenses increased $2.9 million, or 18%, from $15.7 million for the year ended December 31, 2019 to $18.6 million for the year ended December 31, 2020 primarily due to increases of $1.4 million in compensation-related expenses to support the growth of our operations, $1.3 million in legal expenses and $0.8 million in insurance expense, partially offset by a $0.6 million decrease in other expenses, including accounting fees, market research, recruiting fees and travel expense.

Interest Income

Interest income decreased $1.9 million, or 68%, from $2.8 million for the year ended December 31, 2019 to $0.9 million for the year ended December 31, 2020. This decrease was primarily due to the declining interest rate environment 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 increased $0.4 million, or 254%, from $0.2 million for the year ended December 31, 2019 to $0.6 million for the year ended December 31, 2020. Interest expense reflects contractual interest, amortization of origination fees and other issuance costs, and accretion of final payment fees on our term loan that funded in October 2019 and was repaid in full in June 2020.

Income Tax Expense

Income tax expense increased by $2.0 million, or 289%, from an income tax benefit of $0.7 million for the year ended December 31, 2019 to income tax expense of $1.3 million for the year ended December 31, 2020. Our effective income tax rate was (2.0)% for the year ended December 31, 2020 as compared to 0.9% for the year ended December 31, 2019. Our effective income tax rate differs from our federal statutory rate of 21% primarily because our losses cannot 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 is necessary for our Australia subsidiary. Income tax expense for 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. Income tax benefit for the year ended December 31, 2019 included a discrete tax benefit of approximately $1.1 million for the 2017 Australia refundable R&D tax offset.

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 payments under collaboration agreements.

In December 2020, we filed an automatic registration statement on Form S-3ASR and an accompanying prospectus (File No. 333-251254), pursuant to which 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 June 2021, pursuant to the Form S-3ASR (File No. 333-251254), 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. This Form S-3ASR expires in December 2023.

In October 2019, we filed a registration statement on Form S-3 (File No. 333-234414) that was declared effective as of November 22, 2019 and permits the offering, issuance, and sale by us of up to a maximum aggregate offering price of $250.0 million of our common stock, preferred stock, debt securities and warrants (the "2019 Form S-3"). Up to a maximum of $75.0 million of the maximum aggregate offering price of $250.0 million may be issued and sold pursuant to an ATM financing facility under a sales agreement we entered into on November 27, 2019 (the "2019 Sales Agreement"). In May 2020, we completed an underwritten public offering of 7,000,000 shares of 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. During the year ended December 31, 2020, we issued 2,483,719 shares under our ATM facility for net proceeds of $41.9 million. No shares were issued under the ATM facility during the year ended December 31, 2021. As of December 31, 2021, a total of $94.2 million of common stock remained available for sale under the 2019 Form S-3, $31.9 million of which remained available for sale under the ATM financing facility. This Form S-3 expires in October 2022.

We have received $87.5 million in non-refundable payments from Janssen since the inception of the Janssen License and Collaboration Agreement in 2017 through December 31, 2021, as follows:

- Upon effectiveness of the 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; and

- During the fourth quarter of 2021, we received $7.5 million milestone payment from Janssen triggered by completion of the data collection for PN-235 Phase 1 activities.

We also receive payments for services provided under the collaboration agreement and in-kind reimburses Janssen for certain costs they have incurred based on the cost sharing terms of the agreement.

Pursuant to the amended and restated License and Collaboration Agreement with Janssen executed July 27, 2021 (the "Restated Agreement"), we will be eligible to receive clinical development, regulatory and sales milestones, if and as achieved. Upcoming potential development milestones for second-generation products include:

- $25.0 million for dosing of the third patient in the first Phase 2 clinical trial for any second-generation product for any indication; and

- $10.0 million for dosing of the third patient in the first Phase 2 clinical trial for any second-generation product for a second indication.

Capital Requirements

As of December 31, 2021, we had $326.9 million of cash, cash equivalents and marketable securities and an accumulated deficit of $409.4 million. Our capital expenditures were $1.1 million, $0.5 million and $1.0 million for the years ended December 31, 2021, 2020 and 2019, respectively. Our primary uses of cash are to fund operating expenses, primarily our research and development expenditures, general and administrative costs and pre-commercialization costs. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses. We believe, based on our current operating plan and expected expenditures, 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 from the date of this filing. 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 our planned pre-clinical and clinical trials are successful or expanded, our product candidates enter new and more advanced stages of clinical development or our newer product clinical trials or advance beyond the discovery stage. We expect to require additional financing to advance our product candidates through clinical development and toward potential regulatory approval and to develop, acquire or in-license other potential product candidates. Such additional funding may come from raising additional capital, seeking access to debt, and additional collaborative or other arrangements with corporate sources, but such funding may not be available at terms acceptable to us, if at all.

We anticipate that we will need to raise substantial additional funding, the requirements of which will depend on many factors, including:

- the progress, timing, scope, results and costs of our clinical trials and pre-clinical studies for our product candidates, including the ability to enroll patients in a timely manner for our clinical trials;

- the costs of and 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 cost 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 Janssen License and Collaboration Agreement, as amended, or other such arrangements we may enter into, and the timing of receipt of such payments, if any;
- the timing, receipt and amount of royalties under the Janssen License and Collaboration Agreement on worldwide net sales of IL23-R antagonists 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 discovery of product candidates;
- the time and cost necessary to respond to technological and market developments;
- the extent to which we may acquire or in-license other product candidates and technologies;
- 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.

Adequate additional funding may not be available to us on acceptable terms, or at all. 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 will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. If we raise additional capital through debt financing, we may 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.

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

	Year Ended December 31,		
Consolidated Statements of Cash Flows Data:	**2021**	**2020**	**2019**
Cash used in operating activities	$ (107,865)	$ (72,484)	$ (41,527)
Cash used in investing activities	$ (15,860)	$ (90,965)	$ (53,710)
Cash provided by financing activities	$ 129,923	$ 247,626	$ 46,036
Stock-based compensation	$ 16,395	$ 7,899	$ 8,353
(Decrease) increase in deferred revenue - related party	$ (12,876)	$ (27,053)	$ 33,307

Cash Used in Operating Activities

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 used in operating activities for the year ended December 31, 2020 of $72.5 million consisted primarily of our net loss of $66.2 million and net changes of $19.0 million in net operating assets and liabilities, partially offset by certain non-cash items including $7.9 million of stock-based compensation expense and a $1.4 million decrease in deferred tax asset. Changes in net operating assets and liabilities included a $27.1 million decrease in deferred revenue, partially offset by a $5.8 million increase in accrued expenses and other payables and a $4.3 decrease in receivable from collaboration partner. The $31.0 million increase in cash flow used in operating activities during the year ended December 31, 2020, as compared to the year ended December 31, 2019, was primarily due to a $60.4 million change in decrease in deferred revenue, partially offset by an $11.0 million decrease in our net loss, a $15.2 million net increase due to changes in other operating assets and liabilities, and a $2.2 million change in decrease in deferred tax asset.

Cash Used in Investing Activities

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 used in investing activities for the year ended December 31, 2020 was $91.0 million, consisting of purchases of marketable securities of $280.0 million and purchases of property and equipment of $0.5 million, partially offset by proceeds from maturities of marketable securities of $189.5 million. The $37.3 million increase in cash used in investing activities for the year ended December 31, 2020, as compared to the year ended December 31, 2019, was primarily due to an increase of $113.0 million in purchases of marketable securities, partially offset by an increase of $75.3 million of 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, 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 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, and a $3.5 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 $10.5 million related to the early repayment of long-term debt in 2020.

Cash provided by financing activities for the year ended December 31, 2020 was $247.6 million, consisting primarily of cash proceeds from our public offerings of common stock of $213.3 million, cash proceeds from ATM sales of $42.1 million, and proceeds from the issuance of common stock upon exercise of stock options and purchases of common stock under our employee stock purchase plan of $2.8 million, partially offset by early repayment of long-term debt of $10.5 million. The $201.6 million increase in cash provided by financing activities for the year ended December 31, 2020, as compared to the year ended December 31, 2019, was primarily due to an increase of $213.3 million in cash

proceeds from our public offerings of common stock and a $7.6 million increase in cash proceeds from ATM sales, and a decrease of $9.8 million in proceeds received from the issuance of long-term debt, partially offset by $10.5 million related to the repayment of long-term debt in 2021.

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 R&D 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 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 an amendment to our facility lease agreement dated as of March 2017, as amended, 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.

On July 27, 2021, we entered into an amended and restated License and Collaboration Agreement with Janssen. The Restated Agreement amends and restates the License and Collaboration Agreement, dated May 26, 2017, by and between the Company and Janssen (as amended by the First Amendment thereto, effective May 7, 2019). Under the Janssen License and Collaboration 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 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 a Research Collaboration and License Agreement with Zealand Pharma A/S 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. On January 23, 2020, we initiated arbitration proceedings with the International Court of Arbitration of the International Chamber of Commerce against Zealand Pharma A/S. 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 investments.

We had $326.9 million and $307.8 million in cash, cash equivalents and marketable securities at December 31, 2021 and 2020, respectively. 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 increase. Based on our interest rate sensitivity analysis, an immediate 1% increase in interest rates would increase our interest income by approximately $2.2 million, while an immediate 1% decrease in interest rates would decrease our interest income by approximately $0.5 million.

Approximately $1.1 million and $1.0 million of our cash balance was located in Australia at December 31, 2021 and 2020, 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 the 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.

Item 8. Financial Statements and Supplementary Data

PROTAGONIST THERAPEUTICS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Audited Consolidated Financial Statements	**Page**
Report of Independent Registered Public Accounting Firm (PCAOB ID: 42)	74
Report of Independent Registered Public Accounting Firm (PCAOB ID: 238)	77
Consolidated Balance Sheets	78
Consolidated Statements of Operations	79
Consolidated Statements of Comprehensive Loss	80
Consolidated Statements of Stockholders' Equity	81
Consolidated Statements of Cash Flows	82
Notes to the Consolidated Financial Statements	83

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, 2021 and 2020, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2021, 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, 2021 and 2020, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 28, 2022 expressed an unqualified opinion thereon.

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 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. 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 Matters

The critical audit matters communicated below are matters arising from the current period audit of the financial statements that were 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 matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matters below, providing separate opinions on the critical audit matters or on the accounts or disclosures to which they relate.

Accrued clinical and research related expenses

Description of the Matter

At December 31, 2021, the Company has accrued $27.9 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.

Accounting for related party revenue recognition under the Janssen License and Collaboration Agreement

Description of the Matter

As described in Note 3 to the consolidated financial statements, the Company is party to a License and Collaboration Agreement with Janssen Biotech, Inc. (Janssen), which was amended during 2021. The Company re-evaluates the transaction price for this agreement, including variable consideration, at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur. The Company and Janssen make quarterly cost sharing payments to one another in amounts necessary to ensure that each party bears its contractual share of the overall shared costs incurred. The Company utilizes a cost-based input method to measure proportional performance and to calculate the corresponding amount of revenue to recognize each reporting period. For the year ended December 31, 2021, the Company recorded $27.4 million of related party revenue under the License and Collaboration Agreement.

Auditing the Company's revenue recognition for the Janssen agreement is complex due to the judgments made by management in the determination of the transaction price and the calculation of the cost-based input method. The determination of the transaction price and the calculation of the cost-based input method involve subjective estimates of future development costs to be incurred by the Company and by Janssen. Changes to these assumptions can have a material effect on the amount and timing of revenue recognized.

How We Addressed the Matter in Our Audit	Our audit procedures included, among others, evaluating the changes to estimated future development resulting from the 2021 amendment to the agreement. We recomputed revenue recognized and tested the eligibility of research and development costs and appropriateness of FTE costs applied in the determination of the percentage completed under the revenue recognition model. We evaluated the appropriateness of the transaction price based upon estimated payments to be received during the duration of the contract, net of remaining development costs expected to be reimbursed by the Company to Janssen. We met with Company personnel to corroborate our understanding of collaboration developments and activities that have occurred to date. We also tested a sample of cash payments and receipts exchanged between the two parties throughout the year.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2020.
Redwood City, California
February 28, 2022

Report of Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the consolidated statements of operation, comprehensive loss, changes in stockholders' equity and cash flows of Protagonist Therapeutics, Inc. and its subsidiaries (the"Company") for the year ended December 31, 2019, including 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 results of operations and cash flows of the Company for the year ended December 31, 2019 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audit. 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 accordancewith 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 of these consolidated financial statements in accordance with the standards ofthe PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assuranceabout whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audit included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP
San Jose, California
February 28, 2022

We served as the Company's auditor from 2015 to 2019.

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

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 123,665	$ 117,358
Marketable securities	203,235	188,451
Restricted cash - current	—	10
Receivable from collaboration partner and contract asset - related party	1,566	2,426
Research and development tax incentive receivable	2,792	1,084
Prepaid expenses and other current assets	9,478	6,277
Total current assets	340,736	315,606
Marketable securities - noncurrent	—	2,000
Property and equipment, net	1,798	1,462
Restricted cash - noncurrent	225	450
Operating lease right-of-use asset	4,936	4,950
Total assets	$ 347,695	$ 324,468
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 1,600	$ 3,075
Payable to collaboration partner - related party	899	2,732
Accrued expenses and other payables	37,716	18,498
Deferred revenue - related party	1,601	14,477
Operating lease liability - current	2,200	1,459
Total current liabilities	44,016	40,241
Operating lease liability - noncurrent	3,658	4,500
Other liabilities	—	121
Total liabilities	47,674	44,862
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; 47,838,330 and 43,745,465 shares issued and outstanding as of December 31, 2021 and 2020, respectively	—	—
Additional paid-in capital	709,682	563,389
Accumulated other comprehensive (loss) gain	(299)	28
Accumulated deficit	(409,362)	(283,811)
Total stockholders' equity	300,021	279,606
Total liabilities and stockholders' equity	$ 347,695	$ 324,468

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,		
	2021	2020	2019
License and collaboration revenue - related party	$ 27,357	$ 28,628	$ 231
Operating expenses:			
Research and development	126,006	74,506	65,003
General and administrative	27,196	18,638	15,749
Total operating expenses	153,202	93,144	80,752
Loss from operations	(125,845)	(64,516)	(80,521)
Interest income	443	900	2,813
Interest expense	—	(598)	(169)
Loss on early repayment of debt	—	(585)	—
Other expense, net	(149)	(46)	(1)
Loss before income tax (expense) benefit	(125,551)	(64,845)	(77,878)
Income tax (expense) benefit	—	(1,305)	691
Net loss	$ (125,551)	$ (66,150)	$ (77,187)
Net loss per share, basic and diluted	$ (2.71)	$ (1.92)	$ (2.98)
Weighted-average shares used to compute net loss per share, basic and diluted	46,322,910	34,396,446	25,894,024

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,		
	2021	2020	2019
Net loss	$ (125,551)	$ (66,150)	$ (77,187)
Other comprehensive loss:			
(Loss) gain on translation of foreign operations	(182)	266	(44)
Unrealized (loss) gain on marketable securities	(145)	(17)	56
Comprehensive loss	$ (125,878)	$ (65,901)	$ (77,175)

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

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

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Gain	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2018	23,187,219	$ —	$ 253,222	$ (233)	$ (140,474)	$ 112,515
Issuance of common stock pursuant to at-the-market offering, net of issuance costs	2,846,641	—	34,492	—	—	34,492
Issuance of common stock under equity incentive and employee stock purchase plans	583,792	—	1,779	—	—	1,779
Issuance of common stock upon exercise of Exchange Warrants	599,997	—	—	—	—	—
Stock-based compensation expense	—	—	8,353	—	—	8,353
Other comprehensive gain	—	—	—	12	—	12
Net loss	—	—	—	—	(77,187)	(77,187)
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

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,		
	2021	**2020**	**2019**
Cash Flows from Operating Activities			
Net loss	$ (125,551)	$ (66,150)	$ (77,187)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation	16,395	7,899	8,353
Operating lease right-of-use asset amortization	1,962	1,775	1,792
Net amortization of premium (accretion of discount) on marketable securities	1,830	37	(594)
Depreciation and amortization	813	948	732
Change in deferred tax asset	—	1,438	(775)
Loss on early repayment of debt	—	585	—
Gain on disposal of property and equipment	—	—	8
Changes in operating assets and liabilities:			
Research and development tax incentive receivable	(1,775)	(990)	1,411
Receivable from collaboration partner - related party	860	4,329	(2,168)
Prepaid expenses and other assets	(3,227)	(1,102)	(2,820)
Accounts payable	(1,390)	309	(3,000)
Payable to collaboration partner - related party	(1,833)	1,471	201
Accrued expenses and other payables	19,097	5,840	1,098
Deferred revenue - related party	(12,876)	(27,053)	33,307
Operating lease liability	(2,049)	(1,941)	(1,885)
Other liabilities	(121)	121	—
Net cash used in operating activities	(107,865)	(72,484)	(41,527)
Cash Flows from Investing Activities			
Purchase of marketable securities	(286,589)	(280,027)	(166,936)
Proceeds from maturities of marketable securities	271,830	189,533	114,193
Purchases of property and equipment	(1,101)	(471)	(967)
Net cash used in investing activities	(15,860)	(90,965)	(53,710)
Cash Flows from Financing Activities			
Proceeds from public offering of common stock, net of issuance costs	123,829	213,303	—
Proceeds from issuance of common stock upon exercise of stock options and purchases under employee stock purchase plan	6,283	2,799	1,779
Tax withholding payments related to net settlement of restricted stock units	(189)	—	—
Proceeds from at-the-market offering, net of issuance costs	—	42,062	34,492
Early repayment of long-term debt	—	(10,524)	—
Issuance costs related to long-term debt	—	(14)	—
Proceeds from issuance of long-term debt, net of issuance costs	—	—	9,765
Net cash provided by financing activities	129,923	247,626	46,036
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(126)	175	(26)
Net increase (decrease) in cash, cash equivalents and restricted cash	6,072	84,352	(49,227)
Cash, cash equivalents and restricted cash, beginning of period	117,818	33,466	82,693
Cash, cash equivalents and restricted cash, end of period	$ 123,890	$ 117,818	$ 33,466
Supplemental Disclosure of Cash Flow Information:			
Cash paid for interest	$ —	$ 438	$ 70
Supplemental Disclosure of Non-Cash Financing and Investing Information:			
Purchases of property and equipment in accounts payable and accrued liabilities	$ 143	$ 85	$ 100
Issuance costs related to common stock offering included in accrued liabilities and other payables	$ 25	$ 205	$ 80
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.

PROTAGONIST THERAPEUTICS, INC.
Notes to 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 multiple peptide-based investigational new chemical entities in different stages of development, all derived from the Company's proprietary technology platform. 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 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, who is the chief operating decision maker, reviews financial information on an aggregate basis for 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, 2021, the Company had cash, cash equivalents and marketable securities of $326.9 million. The Company has incurred net losses from operations since inception and has an accumulated deficit of $409.4 million as of December 31, 2021. The Company's ultimate success depends on 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 offerings of common stock and payments received under a license and collaboration agreements.

Risks and Uncertainties

The Company is subject to risks and uncertainties as a result of the ongoing COVID-19 pandemic. The Company is continuing to closely monitor the impact of the COVID-19 pandemic on its business and has taken and continues to take proactive efforts to protect the health and safety of its patients, clinical research staff and employees, and to maintain business continuity. The extent of the impact of the COVID-19 pandemic on the Company's activities remains uncertain and difficult to predict, as the response to the pandemic is ongoing and information continues to evolve. Capital markets and economies worldwide have been negatively impacted by the COVID-19 pandemic and may be further impacted in the future. Such economic disruption could have a material adverse effect on the Company's business. Policymakers around the globe have responded with fiscal policy actions to support the healthcare industry and economy as a whole. The magnitude and overall effectiveness of these actions remains uncertain.

The severity of the impact of the COVID-19 pandemic on the Company's activities will depend on a number of factors, including, but not limited to, the duration and severity of the pandemic, including the severity of any additional periods of increases or spikes in the number of cases in the areas the Company its suppliers and its manufacturers operate and areas where the Company's clinical trial sites are located; the development and spread of COVID-19 variants, the timing, extent, effectiveness and durability of COVID-19 vaccine programs or other treatments; and new or continuing travel and other restrictions and public health measures, such as social distancing, business closures or disruptions. Accordingly, the extent and severity of the impact on the Company's existing and planned clinical trials, manufacturing, collaboration activities and operations is uncertain and cannot be fully predicted. The Company has experienced delays in its existing and planned clinical trials due to the worldwide impacts of 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, the ongoing impact on its operating activities and employees, and the ongoing impact of any initiatives or programs that the Company may undertake to address financial and operational challenges. As of the date of issuance of

these consolidated financial statements, the extent to which the COVID-19 pandemic may materially impact the Company's future financial condition, liquidity or results of operations remains uncertain.

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 of America ("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, 2021 and 2020 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 ongoing COVID-19 pandemic, there has been uncertainty and disruption in the global economy and financial markets. The Company has taken into consideration any known COVID-19 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 date of issuance 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 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,		
	2021	2020	2019
Cash and cash equivalents	$ 123,665	$ 117,358	$ 33,006
Restricted cash - current	—	10	10
Restricted cash - noncurrent	225	450	450
Total cash reported on consolidated statements of cash flows	$ 123,890	$ 117,818	$ 33,466

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, receivable from collaboration partner, accounts payable, payable to 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 adopted Accounting Standards Codification Topic 842, *Leases,* ("ASC 842") effective January 1, 2019. The Company determines if an arrangement is a lease at inception. Pursuant to 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 will be 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 is used, it 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, and 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).

The period between when the Company transfers control of promised goods or services and when the Company receives payment is expected to be one year or less, which is consistent with the Company's historical experience. Upfront payment contract liabilities resulting from the Company's license and collaboration agreements do not represent a financing component as the payment is not financing the transfer of goods and services, and the technology underlying the licenses granted reflects research and development expenses already incurred by the Company. As such, the Company does not adjust its revenues for the effects of a significant financing component.

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.

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 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, number of patients enrolled, the rate of patient enrollment and number and location of sites activated may vary from the Company's estimates, resulting in adjustments to expense 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.

The Company has received orphan drug designation from the U.S. Food and Drug Administration ("FDA") for its clinical asset rusfertide (generic name for 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.

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.

Small Business Innovation Research ("SBIR") Grants

The Company has received SBIR grants from the National Institutes of Health ("NIH") in support of its research activities. The Company recognizes a reduction to research and development expenses when expenses related to grants have been incurred and the grant funds become contractually due from NIH.

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 outstanding during the period, without consideration of potentially dilutive securities. In accordance with Accounting Standards Codification Topic 260, *Earnings Per Share*, the 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 Adopted Accounting Pronouncements

In December 2019, the FASB issued Accounting Standards Update ("ASU") No. 2019-12, Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes, which removes certain exceptions and amends certain requirements in the existing income tax guidance to ease accounting requirements. This guidance is effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2020 and must be applied on a retrospective basis. The Company adopted this guidance effective January 1, 2021 and there was no impact on its consolidated financial statements and disclosures.

Recently Issued Accounting Pronouncements Not Yet Adopted as of December 31, 2021

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments - Credit Losses (Topic 326)*, which is intended to provide financial statement users with 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 within those years beginning after December 15, 2019, with early adoption permitted for fiscal years and interim periods within those years 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 is currently evaluating the impact of this new guidance on its consolidated financial statements and 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 ("Restated Agreement") with Janssen Biotech, Inc., a Pennsylvania corporation ("Janssen"). The Restated Agreement amends and restates the License and Collaboration Agreement, dated May 26, 2017, by and between the Company and Janssen (as amended by the First Amendment thereto, effective May 7, 2019, the "Original Agreement"). 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. The Original Agreement became effective on July 13, 2017. 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 also 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 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 PN-235 (JNJ-77242113). PTG-200 was an oral IL-23

receptor antagonist in 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 PN-235, based on its superior potency and overall pharmacokinetic and pharmacodynamic profile. Janssen is primarily responsible for the conduct of all future trials, including these anticipated Phase 2 trials, and the Company is primarily responsible for the conduct of the second-generation Phase 1 studies.

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 study, and the Phase 1 studies in PN-232 and PN-235; 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 studies 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); (c) up to $25.0 million in costs related to up to two Phase 2 studies evaluating second-generation compounds.

The Company's continuing development expense obligations under the Restated Agreement were as follows: (a) the Company funded 20% of the costs related to the Phase 2a study 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 study evaluating PN-235 incurred through January 4, 2021; (c) the Company was responsible for 100% of agreed-upon costs related to the Phase 1 study evaluating PN-232.

Certain of the Company's previous development expense 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 studies 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 study evaluating a second-generation compound was eliminated; and (c) the Company had no obligation to fund any portion of any Phase 2b or other study evaluating PTG-200 beyond the Phase 2a study 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 now 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 could 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:

- $25.0 million for dosing of the 3rd patient in the first Phase 2 clinical trial for any second-generation compound for any indication;
- $10.0 million for dosing of the 3rd 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 described above);
- $50.0 million for dosing of the 3rd patient in a Phase 3 clinical trial for a second-generation compound for any indication;
- $15.0 million for dosing of the 3rd patient in a Phase 3 clinical trial for a second-generation compound for a second indication; and
- $115.0 million for 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 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 PN-235 through Phase 1. Under the Restated Agreement, development services performed by the Company for PTG-200 beyond Phase 2a and PN-232 and PN-235 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 PN-235 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 is 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.

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 Company determined that the duration of the Restated Agreement for the identified single initial performance obligation began on the Original Agreement effective date of July 13, 2017 and ends upon the later of the end of Phase 2a for PTG-200 in CD or the completion of a Phase 1 clinical trial for either PN-232 or PN-235. Final activities related to the PTG-200 Phase 2a trial, PN-235 Phase 1 trial and PN-232 Phase 1 trial are expected to be completed in early 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 $106.5 million as of December 31, 2021, an increase of $7.9 million from the transaction price of $98.6 million at December 31, 2020 under the Original Agreement and a decrease of $6.4 million from the transaction price of $112.9 million at December 31, 2019 under the Original Agreement. In order to determine the transaction price, the Company 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, 2021 includes $87.5 million of nonrefundable payments received to date, $17.9 million of reimbursement from Janssen for services performed for IL-23 receptor antagonist compound research costs and other services, and estimated variable consideration consisting of $8.2 million of development cost reimbursement receivable from Janssen, partially offset by $7.1 million of net cost reimbursement due to Janssen for services performed. The Company evaluated whether the variable component of the transaction price should be constrained to ensure that a significant reversal of revenue recognized on a cumulative basis as of December 31, 2021 is not probable. The Company concluded that the variable consideration constraint is appropriately reflected in the estimated transaction price as of December 31, 2021, 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, 2021 that a material reversal of such revenues would not occur. Janssen also opted in for certain additional services to be performed by the Company that are outside the initial performance obligation, revenue is recognized as these services are performed.

The Company re-evaluates the transaction price, including variable consideration, at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur. The Company and Janssen make quarterly cost sharing payments to one another in amounts necessary to ensure that each party bears its contractual share of the overall shared costs incurred.

The Company utilizes 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 uses actual costs incurred relative to expected costs to fulfill the combined performance obligation. These costs consist primarily of internal FTE effort and third-party contract costs. Revenue will be recognized based on actual costs incurred as a percentage of total estimated costs as the Company completes 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. In making such estimates, significant judgment is required to evaluate assumptions related to cost estimates. The cumulative effect of revisions to estimated costs to complete the Company's performance obligations will be recorded in the period in which changes are identified and amounts can be reasonably estimated. A significant change in these assumptions and estimates could have a material impact on the timing and amount of revenue recognized in future periods.

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 contract modification for the Restated Agreement. In addition, the Company recorded $0.8 million of revenue related to additional services provided by the Company under the agreement.

For the year ended December 31, 2020, the Company recognized $28.6 million of license and collaboration revenue. This amount included a $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 Janssen License and Collaboration 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 Janssen License and Collaboration Agreement.

For the year ended December 31, 2019, the Company recognized $0.2 million of license and collaboration revenue. This amount included a $9.4 million cumulative catchup adjustment as a reduction of revenue, offset by $8.0 million of license and collaboration revenue recognized following the contract modification for the First Amendment to the agreement and $1.6 million of collaboration revenue recognized during the first quarter of 2019 prior to the effectiveness of the First Amendment. No revenue for additional services was recognized for the year ended December 31, 2019.

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

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

Year Ended December 31, 2020	Balance at Beginning of Period	Additions	Deductions	Balance at End of Period
Contract assets:				
Receivable from collaboration partner - related party	$ 5,955	$ 6,221	$ (9,750)	$ 2,426
Contract asset - related party	$ 800	$ 342	$ (1,142)	$ —
Contract liabilities:				
Deferred revenue - related party	$ 41,530	$ 3,963	$ (31,016)	$ 14,477
Payable to collaboration partner - related party	$ 1,262	$ 3,800	$ (2,330)	$ 2,732

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 revenue of $14.1 million from amounts included in the deferred revenue balance at the beginning of the year. During the year ended December 31, 2019, the Company recognized $1.6 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 table presents the fair value of the Company's financial assets determined using the inputs defined above (in thousands).

	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

	December 31, 2020			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$ 27,481	$ —	$ —	$ 27,481
Commercial paper	—	65,863	—	65,863
Corporate debt securities	—	27,590	—	27,590
U.S. Treasury and agency securities	—	183,210	—	183,210
Total financial assets	$ 27,481	$ 276,663	$ —	$ 304,144

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 are 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.

Note 5. Cash Equivalents and Marketable Securities

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

	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 - current				203,235
Marketable securities - noncurrent				—
Total cash equivalents and marketable securities				$ 318,570

	December 31, 2020			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Money market funds	$ 27,481	$ —	$ —	$ 27,481
Commercial paper	65,866	—	(3)	65,863
Corporate debt securities	27,592	2	(4)	27,590
U.S. Treasury and agency securities	183,203	10	(3)	183,210
Total cash equivalents and marketable securities	$ 304,142	$ 12	$ (10)	$ 304,144
Classified as:				
Cash equivalents				$ 113,693
Marketable securities - current				188,451
Marketable securities - noncurrent				2,000
Total cash equivalents and marketable securities				$ 304,144

Marketable securities – current of $203.2 million and $188.5 million held at December 31, 2021 and 2020, respectively, had contractual maturities of less than one year. Marketable securities – noncurrent of $2.0 million held at December 31, 2020 had contractual maturities of at least one year but less than two years. The Company did not hold any marketable securities – noncurrent at December 31, 2021. 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. There were no realized gains or realized losses on marketable securities for the periods presented. 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.

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,	
	2021	2020
Prepaid clinical and research related expenses	$ 5,242	$ 3,517
Prepaid insurance	1,746	1,440
Other prepaid expenses	1,515	1,009
Other receivable	975	311
Prepaid expenses and other current assets	$ 9,478	$ 6,277

Property and Equipment, Net

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

	December 31,	
	2021	2020
Laboratory equipment	$ 4,156	$ 3,539
Furniture and computer equipment	1,023	648
Leasehold improvements	877	748
Total property and equipment	6,056	4,935
Less: accumulated depreciation	(4,258)	(3,473)
Property and equipment, net	$ 1,798	$ 1,462

Depreciation expense for the years ended December 31, 2021, 2020 and 2019, was $813,000, $789,000 and $703,000, respectively. As of December 31, 2021, 2020 and 2019, $262,000, $46,000 and $37,000, 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,	
	2021	2020
Accrued clinical and research related expenses	$ 27,950	$ 11,335
Accrued employee related expenses	7,125	6,413
Accrued professional service fees	734	668
Accrued collaboration payments	1,500	—
Other	407	82
Total accrued expenses and other payables	$ 37,716	$ 18,498

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 expenses 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, 2020 or 2019.

Note 8. Government Programs

Research and Development Tax Incentive

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. During the year ended December 31, 2019, the Company recognized AUD 1.9 million ($1.3 million) of research and development expenses in connection with the research and development tax incentive from the ATO because the Company determined that it had exceeded the annual turnover limit to claim such amounts following the receipt of certain payments under the Janssen License and Collaboration Agreement. 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.

Small Business Innovation Research ("SBIR") Grants

In May 2017, the Company was awarded a Phase 2 SBIR grant from the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH in support of research aimed at developing biomarkers that define IL-23R target engagement by orally delivered peptide antagonists and the effects of that engagement of downstream signaling. The total grant award was $1.3 million and was originally for the period from May 2017 to April 2019. During the year ended December 31, 2019, the Company requested and received an extension of this grant through April 2020.

In September 2018, the Company was awarded a Phase 2 SBIR Grant from the National Heart, Lungs and Blood Institute of the NIH in support of research aimed at developing the Company's novel hepcidin mimetic rusfertide for the potential treatment of chronic anemia and iron overload in rare blood disorders, including beta-thalassemia. The total grant award was $1.5 million and was originally for the period from September 2018 to August 2020. During the year ended December 31, 2020, the Company requested an extension of this grant through July 2021, which was received in February 2021.

The Company recognizes a reduction to research and development expenses when expenses related to the grants have been incurred and the grant funds become contractually due from NIH. The Company recorded $0.5 million and $1.4 million as a reduction of research and development expenses for the years ended December 31, 2020 and 2019, respectively. No such amount was recorded during the year ended December 31, 2021. As of December 31, 2021, the Company has received all grant funds contractually due from NIH for these completed SBIR grants.

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.

The Term Loans were subject to an origination fee of 0.25% for each funded tranche under the Term Loan Credit Agreement and bore interest at an annual rate based on prime rate plus 2.91%, subject to a prime rate floor of 4.94%. The Company would make interest-only payments on the Term Loans for 24 months, followed by 24 months of principal and interest payments. At the Company's option, the Company could prepay the outstanding principal balance of the Term Loans in whole or in part, subject to a prepayment premium of 3.0% of any amount prepaid if the prepayment occurred through and including the first anniversary of the closing date, 2.0% of the amount prepaid if the prepayment occurred after the first anniversary of the closing date through and including the second anniversary of the closing date, and 1.0% of any amount prepaid after the second anniversary of the closing date and prior to October 1, 2023. An additional fee of 2.85% of the amount of Term Loans advanced by the Lenders was due upon prepayment or repayment of the Term Loans.

The Term Loan Credit Agreement required the Company to maintain cash and cash equivalents of at least 35% of the outstanding Term Loans at all times and was secured by a perfected security interest in all of the Company's assets except for intellectual property and certain other customary excluded property pursuant to the terms of the Term Loan Credit Agreement. The Term Loan Credit Agreement contained other covenants that limited the Company's ability and the ability of its subsidiaries to perform certain actions, including obligations to not pay dividends and to maintain unrestricted cash balances above certain threshold, non-occurrence of material adverse change, non-occurrence of change of control and other customary affirmative and negative covenants. The violation of any provision of covenants would result in default for the Company. The Term Loan Credit Agreement included a clause which allowed lenders to accelerate repayment upon the occurrence of certain events of default.

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, and therefore had no outstanding balance as of December 31, 2020 related to the Term Loan Credit Agreement.

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. As a result, the Company had no outstanding balance and no obligations related to the Term Loan Credit Agreement as of December 31, 2021.

The Company recognized $0.6 million and $0.2 million in interest expense related to the Term Loans during the years ended December 31, 2020 and 2019, respectively. No interest expense related to the Term Loans was recognized during the year ended December 31, 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 an amendment (the "Second Amendment") to its original facility lease agreement for 15,000 square feet of additional office space in Newark, California. 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:	**2021**	**2020**
Operating lease right-of-use asset	$ 4,936	$ 4,950
Operating lease liability - current	$ 2,200	$ 1,459
Operating lease liability - noncurrent	3,658	4,500
Total operating lease liabilities	$ 5,858	$ 5,959
Weighted-average remaining lease term (years)	2.4	3.4
Weighted-average discount rate	10.4%	11.0%

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

	Year Ended December 31,		
	2021	**2020**	**2019**
Operating lease cost	$ 1,962	$ 1,775	$ 1,792
Less: Sublease income	(91)	(89)	(64)
Total lease expense	$ 1,871	$ 1,686	$ 1,728

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

	Year Ended December 31,		
	2021	**2020**	**2019**
Operating cash flow used by operating leases	$ 2,049	$ 1,941	$ 1,885
New operating lease asset obtained in exchange for operating lease liability	$ 1,373	$ —	$ —

Future lease payments required under lease obligations as of December 31, 2021 are as follows (in thousands):

Year Ending December 31:	Amount
2022	$ 2,660
2023	2,744
2024	1,160
2025	—
Thereafter	—
Total future minimum lease payments	6,564
Less: imputed interest	(706)
Present value of lease liabilities	$ 5,858

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 R&D 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 California corporate 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 is 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 have been reduced by 50%, except that the Company agreed to pay in full within two (2) business days after the effective date of the 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 rate payable by the Company on net sales of rusfertide has been reduced by 50%; (4) all sales milestone payments on net sales of rusfertide have been 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 have 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 research and development project; as such, payments or milestone payments were recorded as research and development expenses. As a result, no accruals related to legal proceedings were recognized as of December 31, 2021.

Note 12. Stockholders' Equity

In September 2017, the Company filed a registration statement on Form S-3 with the Securities and Exchange Commission (File No. 333-220314) that was declared effective as of October 5, 2017 and permitted the offering, issuance, and sale by the Company of up to a maximum aggregate offering price of $200.0 million of its common stock, preferred stock and certain debt securities (the "2017 Form S-3"). Up to a maximum of $50.0 million of the maximum aggregate offering price of $200.0 million could be issued and sold pursuant to an at-the-market ("ATM") financing facility under a sales agreement (the "2017 Sales Agreement"). The 2017 Sales Agreement was terminated in 2019. During the year ended December 31, 2019, prior to the termination of the 2017 Sales Agreement, the Company sold 2,846,641 shares of its common stock for net proceeds of $34.5 million, after deducting issuance costs. The 2017 Form S-3 expired in October 2020.

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, 2021, 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 will 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. 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 are 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 is 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 were net exercised, resulting in the issuance of 599,997 shares of common stock. As of December 31, 2021, 400,000 of the Exchange Warrants remain unexercised.

In October 2019, the Company filed a registration statement on Form S-3 (File No. 333-234414) that was declared effective as of November 22, 2019 and permits the offering, issuance, and sale by the Company of up to a maximum aggregate offering price of $250.0 million of its common stock, preferred stock, debt securities and warrants (the "2019 Form S-3"). Up to a maximum of $75.0 million of the maximum aggregate offering price of $250.0 million may be issued and sold pursuant to an ATM financing facility under a sales agreement entered into by the Company on November 27, 2019 (the "2019 Sales Agreement"). 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. The Company sold 2,483,719 shares of its common stock pursuant to the 2019 Sales Agreement during the year ended December 31, 2020 for net proceeds of $41.9 million, after deducting issuance costs. As of December 31, 2021, a total of $94.2 million of common stock remained available for sale under the 2019 Form S-3, $31.9 million of which remained available for sale under the ATM financing facility. The 2019 Form S-3 expires in October 2022.

In December 2020, the Company filed an automatic registration statement on Form S-3ASR and an accompanying prospectus (File No. 333-251254), pursuant to which 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, pursuant to the Form S-3ASR (File No. 33-251254), 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. The Form S-3ASR expires in December 2023.

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, 2021, approximately 564,189 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 it reserved and authorized 750,000 shares of the Company's common stock in order to award 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, 2021, approximately 243,125 shares were available for issuance under the 2018 Inducement Plan.

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, 2020	4,648,120	$ 11.87	7.61	$ 40.0
Options granted	1,949,940	29.96		
Options exercised	(474,801)	11.34		
Options forfeited	(232,719)	17.84		
Balances at December 31, 2021	5,890,540	$ 17.66	7.47	$ 102.7
Options exercisable – December 31, 2021	3,224,575	$ 13.13	6.38	$ 68.1
Options vested and expected to vest – December 31, 2021	5,890,540	$ 17.66	7.47	$ 102.7

(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, 2021. The calculation excludes options with an exercise price higher than the closing price of the Company's common stock on December 31, 2021.

The aggregate intrinsic value of options exercised was $10.5 million, $3.0 million and $2.6 million for the years ended December 31, 2021, 2020 and 2019, respectively.

During the years ended December 31, 2021, 2020 and 2019, the estimated weighted-average grant-date fair value of common stock underlying options granted was $21.94, $7.76 and $5.45 per share, respectively.

For the years ended December 31, 2021, 2020 and 2019, the aggregate fair value of stock options that vested during the year was $11.3 million, $7.1 million and $7.3 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,		
	2021	**2020**	**2019**
Expected term (in years)	5.27- 6.08	5.27- 6.08	5.00 - 6.08
Expected volatility	87.4% - 95.2%	72.1% - 87.5%	61.0% - 64.8%
Risk-free interest rate	0.11% - 1.35%	0.23% - 1.44%	1.42% - 2.58%
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— Prior to January 1, 2020, the Company's expected volatility was estimated based on the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the awards. Beginning January 1, 2020, the Company's expected volatility is based upon a blend of 75% of the average volatility for comparable publicly traded biopharmaceutical companies and 25% of the volatility of the Company's stock price since its initial public offering in August 2016. Beginning January 1, 2021, the Company's expected volatility is 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.

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

The Company began issuing restricted stock units under the 2016 Plan during the year ended December 31, 2018. A restricted stock unit is an agreement to issue shares of the Company's common stock at the time of vesting. Restricted stock unit awards generally vest in four equal installments on approximately the first, second, third and fourth anniversaries of the grant date. Restricted stock unit awards granted to certain executives in 2021 vest 100% on the third anniversary of the grant date. Restricted stock unit incentive awards granted during 2018 vested in three equal installments at six months intervals over a period of 18 months.

Restricted stock unit 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, 2020	244,545	$	9.31
Granted	302,250		24.40
Vested	(78,165)		10.13
Forfeited	(62,658)		18.65
Unvested RSUs at December 31, 2021	405,972	$	20.13

Stock-based compensation expense associated with restricted stock units 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 restricted stock units, the Company recognizes compensation expense over the vesting period of the awards that are ultimately expected to vest.

For the years ended December 31, 2021, 2020 and 2019, the aggregate fair value of restricted stock units that vested during the year was $0.8 million, $1.2 million and $1.8 million, respectively.

Performance Stock Units

Performance stock unit 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, 2020	—		
Granted	110,500	$	23.57
Vested	—		—
Forfeited	(5,000)		23.57
Unvested PSUs at December 31, 2021	105,500	$	23.57

During the first quarter of 2021, the Company granted 110,500 PSUs to certain executives of the Company pursuant to the terms of the 2016 Plan. The grant date fair value of the PSUs was $23.57 per share. The terms of the 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 expire five years from the grant date if the performance objectives are not achieved. 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 outstanding PSUs as of December 31, 2021 was $2.5 million. As of December 31, 2021, the achievement of the related performance objective was deemed not probable and, accordingly, no stock-based compensation for the PSUs has been recognized as expense as of December 31, 2021.

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, 2021, a total of 43,648 shares were issued under the 2016 ESPP, and 1,013,999 shares remain available for issuance as of December 31, 2021.

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,		
	2021	2020	2019
Expected term (in years)	0.50	0.50	0.50
Expected volatility	50.9% - 69.7%	89.1% - 120.4%	58.9% - 65.3%
Risk-free interest rate	0.06%	0.12% - 0.43%	1.89% - 2.32%
Dividend yield	—	—	—

Stock-Based Compensation

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

	Year Ended December 31,		
	2021	2020	2019
Research and development	$ 8,996	$ 4,121	$ 4,350
General and administrative	7,399	3,778	4,003
Total stock-based compensation expense	$ 16,395	$ 7,899	$ 8,353

As of December 31, 2021, total unrecognized stock-based compensation expense was approximately $46.3 million, which the Company expects to recognize over a weighted-average period of approximately 2.7 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. For the year ended December 31, 2021, the Company matched 50% of each employee's contribution up to a maximum of $3,500, resulting in recognized expense of approximately $0.3 million relating to these contributions. No matching contributions were made to the plan by the Company for the years ended December 31, 2020 and 2019.

Note 15. Income Taxes

No income tax expense was recorded by the Company for the year ended December 31, 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 Company recorded an income tax benefit of $0.7 million for the year ended December 31, 2019 primarily due to research and development tax credits and the recognition of deferred tax assets in the Company's Australia subsidiary.

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

	Year Ended December 31,		
	2021	2020	2019
Domestic	$ (125,797)	$ (71,073)	$ (72,271)
Foreign	246	6,228	(5,607)
Total net loss before taxes	$ (125,551)	$ (64,845)	$ (77,878)

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

	Year Ended December 31,		
	2021	2020	2019
Current:			
Federal	$ —	$ —	$ —
State	—	—	—
Foreign	—	(88)	84
Total current tax (benefit) expense	—	(88)	84
Deferred:			
Federal	—	—	—
State	—	—	—
Foreign	—	1,393	(775)
Total deferred tax expense (benefit)	—	1,393	(775)
Total income tax expense (benefit)	$ —	$ 1,305	$ (691)

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

	Year Ended December 31,		
	2021	2020	2019
Federal statutory income tax rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal benefit	1.9	1.9	1.2
Research and development credits	4.3	6.5	4.3
Foreign tax rate difference	—	(0.9)	0.7
Change in valuation allowance	(28.0)	(34.3)	(23.8)
Other	0.8	3.8	(2.5)
(Provision) benefit for income taxes	— %	(2.0)%	0.9 %

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

	December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 75,649	$ 50,272
Depreciation and amortization	1,153	1,237
Accruals/other	5,716	5,332
Operating lease liability	1,230	1,252
Research and development and foreign credits	21,197	14,856
Total deferred tax assets	104,945	72,949
Deferred tax liabilities:		
Operating right-of-use asset	(1,037)	(1,040)
Total deferred tax liabilities	(1,037)	(1,040)
Valuation allowance	(103,908)	(71,909)
Net deferred tax assets	$ —	$ —

Realization of the deferred tax assets is dependent upon future taxable income, if any, the amount and timing of which are uncertain. The Company established a valuation allowance to offset U.S. deferred tax assets as of December 31, 2021, 2020 and 2019 due to the uncertainty of realizing future tax benefits from its net operating loss carryforwards and other deferred tax assets. The Company also established a valuation allowance to offset Australian deferred tax assets as of December 31, 2021. The valuation allowance increased by approximately $32.0 million, $19.4 million and $18.5 million during the years ended December 31, 2021, 2020 and 2019, 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, 2021. 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.

At December 31, 2021, the Company had $347.7 million of federal net operating loss carryforwards and $336.2 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 $269.0 million have no expiration date. The state net operating loss carryforwards will begin to expire in 2035, if not utilized.

At December 31, 2021, the Company also had fully utilized the remaining Australian tax losses of AUD 3.1 million ($2.3 million) carryforward.

As of December 31, 2021, the Company had $19.2 million of federal and $7.9 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, 2021, the Company had AUD 2.9 million ($2.1 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,		
	2021	2020	2019
Balance at beginning of year	$ 19,885	$ 16,631	$ 9,466
(Decreases) increases based on tax positions related to prior years	—	(3,799)	184
Increases based on tax positions related to current year	13,274	7,053	6,981
Balance at end of year	$ 33,159	$ 19,885	$ 16,631

At December 31, 2021, the Company had unrecognized tax benefits of $33.2 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, 2021, 2020 and 2019.

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, 2021 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.

Note 16. Net Loss per Share

As the Company had a net loss for the years ended December 31, 2021, 2020 and 2019, 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,		
	2021	2020	2019
Numerator:			
Net loss	$ (125,551)	$ (66,150)	$ (77,187)
Denominator:			
Weighted-average shares used to compute net loss per common share, basic and diluted	46,322,910	34,396,446	25,894,024
Net loss per share, basic and diluted	$ (2.71)	$ (1.92)	$ (2.98)

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,		
	2021	2020	2019
Options to purchase common stock	5,890,540	4,648,120	3,681,521
Common stock warrants	2,750,000	2,750,000	2,750,000
Restricted stock units	405,972	244,545	278,482
Performance stock units	105,500	—	—
ESPP shares	18,055	28,445	40,275
Total	9,170,067	7,671,110	6,750,278

Note 17. Restructuring

On May 7, 2020, the Company approved a limited reduction in force plan affecting approximately 12% of the Company's employee base and informed the affected employees. The reduction-in-force plan was completed by the end of the second quarter of 2020. Total cash expenditures for the reduction in force plan were $0.3 million, substantially all of which were related to employee severance and benefits costs.

Note 18. Subsequent Event

The Company sold 422,367 shares of its common stock under its ATM financing facility pursuant to the 2019 Sales Agreement during the period from January 1, 2022 through the date of issuance of this Annual Report on Form 10-K. Net proceeds were $14.6 million, after deducting issuance costs. As of the date of issuance of this Annual Report on Form 10-K, a total of $79.3 million of common stock remained available for sale under the 2019 Form S-3, $17.0 million of which remained available for sale under the ATM financing 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, 2021. 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, 2021 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, 2021.

Our independent registered public accounting firm, Ernst & Young LLP, has audited the effectiveness of our internal control over financial reporting as of December 31, 2021 as stated in their attestation report which is included herein.

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.

Report of Independent Registered Public Accounting Firm

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

Opinion on Internal Control over Financial Reporting

We have audited Protagonist Therapeutics, Inc.'s internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Protagonist Therapeutics, Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the two years in the period ended December 31, 2021, and the related notes, and our report dated February 28, 2022 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's annual report on internal control over financial reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the 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 audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.

Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

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

/s/ Ernst & Young LLP

Redwood City, California
February 28, 2022

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 by reference from our definitive Proxy Statement, under the headings "Proposal 1 – Election of Directors," "Executive Officers," "Director Compensation – Equity Compensation Plan Information" and, if applicable, "Delinquent Section 16(a) Reports," to be filed with the SEC in connection with our 2022 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2021.

We have adopted a Code of Business Conduct and Ethics that applies to all directors, officers and employees, including our principal executive officer and principal financial officer. 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 by reference from our definitive Proxy Statement, under the headings "Information Regarding the Committees of the Board of Directors – Compensation Committee," "– Compensation Committee Interlocks and Insider Participation" and "Executive Compensation," to be filed with the SEC in connection with our 2022 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2021.

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

The information required by this item is incorporated by reference from our definitive Proxy Statement, under the heading "Security Ownership of Certain Beneficial Owners and Management," to be filed with the SEC in connection with our 2022 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2021.

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

The information required by this item is incorporated by reference from our definitive 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," to be filed with the SEC in connection with our 2022 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 20, 2021.

Item 14. Principal Accounting Fees and Services

The information required by this item is incorporated by reference from our definitive Proxy Statement, under the heading "Proposal 2 – Ratification of Selection of Independent Registered Public Accounting Firm," to be filed with the SEC in connection with our 2022 Annual Meeting of Stockholders within 120 days after the end of the fiscal year ended December 31, 2021.

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	8/1/2016	
4.1	Specimen stock certificate evidencing the shares of common stock	S-1/A	333-212476	4.1	8/1/2016	
4.2	Third Amended and Restated Investor Rights Agreement, by and among Protagonist Therapeutics, Inc. and the stockholders named therein, dated July 31, 2016.	S-1/A	333-212476	4.2	8/1/2016	
4.3	Form of Indenture	S-3	333-251254	4.3	12/10/2020	
4.4	Form of Common Stock Warrant	S-3	333-251254	4.5	12/10/2020	
4.5	Form of Preferred Stock Warrant	S-3	333-251254	4.6	12/10/2020	
4.6	Form of Debt Securities Warrant	S-3	333-251254	4.7	12/10/2020	
4.7	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	

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed Herewith
		Form	SEC File No.	Exhibit	Filing Date	
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+	Amended and Restated Protagonist Therapeutics, Inc. 2018 Inducement Plan, form of stock option grant notice, form of option agreement, form of restricted stock unit grant notice and form of restricted stock unit agreement.	8-K	001-37852	10.1	2/24/2020	
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	
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	

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed Herewith
		Form	SEC File No.	Exhibit	Filing Date	
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	
10.20+	Offer Letter, by and between Protagonist Therapeutics Inc. and Donald Kalkofen, dated May 20, 2019.	8-K	001-37852	10.1	5/29/2019	
10.21	Credit and Security Agreement, dated October 30, 2019, by and between Protagonist Therapeutics, Inc., MidCap Financial, and Silicon Valley Bank.	10-K	001-37852	10.25	3/10/2020	
10.22	Open Market Sale Agreement℠, dated November 27, 2019, by and between Protagonist Therapeutics, Inc. and Jefferies LLC.	8-K	001-37852	10.1	11/27/2019	
10.23+	Severance Agreement, dated August 4, 2020, by and between Protagonist Therapeutics, Inc. and Donald Kalkofen.	10-Q	001-37852	10.1	8/6/2020	
10.24†	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	
10.25†	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	
10.26†	Second Amendment to Lease, dated August 10, 2021, 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	
21.1	List of Subsidiaries					X

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed Herewith
		Form	SEC File No.	Exhibit	Filing Date	
23.1	Consent of Ernst & Young LLP, Independent Registered Public Accounting Firm					X
23.2	Consent of PricewaterhouseCoopers LLP, 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
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					X

+ Indicates management contract or compensatory plan, contract or agreement.
† Confidential treatment has been granted for a portion of this exhibit.

* 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.

\# Portions of this exhibit (indicated by hashtag) have been omitted as the registrant has determined that (i) the omitted information is not material and (ii) the omitted information would likely cause competitive harm to the registrant if publicly disclosed.

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: February 28, 2022

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 Don Kalkofen, 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)*	February 28, 2022
/s/ Don Kalkofen Don Kalkofen	Chief Financial Officer *(Principal Financial and Accounting Officer)*	February 28, 2022
/s/ Harold E. Selick, Ph.D. Harold E. Selick, Ph.D.	Chairman of the Board of Directors	February 28, 2022
/s/ Bryan Giraudo Bryan Giraudo	Director	February 28, 2022
/s/ Sarah Noonberg, M.D., Ph.D. Sarah Noonberg, M.D., Ph.D.	Director	February 28, 2022
/s/ Sarah O'Dowd Sarah O'Dowd	Director	February 28, 2022
/s/ William D. Waddill William D. Waddill	Director	February 28, 2022
/s/ Lewis T. Williams, M.D., Ph.D. Lewis T. Williams, M.D., Ph.D.	Director	February 28, 2022

Exhibit 4.7

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

The following is a description of the authorized capital stock of Protagonist Therapeutics, Inc., a Delaware Corporation ("we," "us," "our," or the "Company"). The following summaries and descriptions are not complete and are subject to and qualified by reference to the actual provisions of the Company's Amended and Restated Certificate of Incorporation (the "Charter") and Amended and Restated Bylaws (the "Bylaws"), both of which have been filed with the Securities and Exchange Commission and are incorporated by reference herein. We encourage you to read our Charter, our Bylaws, and the applicable provisions of the Delaware General Corporation Law for more information.

General

Pursuant to the Company's Charter, the Company is authorized to issue up to 90,000,000 shares of common stock, par value $0.00001 per share (the "Common Stock"), and up to 10,000,000 shares of preferred stock, par value $0.00001 per share (the Preferred Stock"). As of December 31, 2021, there were 47,838,330 shares of our Common Stock were issued and outstanding. No Preferred Stock is currently outstanding.

Common Stock

Voting Rights

Holders of our Common Stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders, including the election of directors, and do not have cumulative voting rights. Accordingly, the holders of a majority of the outstanding shares of Common Stock entitled to vote in any election of directors can elect all of the directors standing for election, if they so choose, other than any directors that holders of any Preferred Stock we may issue may be entitled to elect.

Dividend Rights

Subject to preferences that may be applicable to any then outstanding Preferred Stock, holders of Common Stock are entitled to receive ratably those dividends, if any, as may be declared by the board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, the holders of Common Stock will be entitled to share ratably in the assets legally available for distribution to stockholders after the payment of or provision for all of our debts and other liabilities, subject to the prior rights of any Preferred Stock then outstanding.

Rights and Preferences

Holders of Common Stock have no preemptive or conversion rights or other subscription rights and there are no redemption or sinking funds provisions applicable to the Common Stock. The rights, preferences and privileges of holders of Common Stock are subject to and may be adversely affected by the rights of the holders of shares of any series of Preferred Stock that we may designate and issue in the future.

Anti-Takeover Effects of Delaware Law and our Certificate of Incorporation and Bylaws

Some provisions of Delaware law, our certificate of incorporation and our bylaws contain provisions that could make the following transactions more difficult: an acquisition of us by means of a tender offer; an acquisition of us by means of a proxy contest or otherwise; or the removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult to accomplish or could deter transactions that stockholders may otherwise

consider to be in their best interest or in our best interests, including transactions which provide for payment of a premium over the market price for our shares.

These provisions, summarized below, are intended to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of the increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

Undesignated Preferred Stock—The ability to authorize undesignated Preferred Stock makes it possible for our board of directors to issue Preferred Stock with voting or other rights or preferences that could impede the success of any attempt to change control of us. These and other provisions may have the effect of deterring hostile takeovers or delaying changes in control or management of our company.

Stockholder Meetings—Our bylaws provide that a special meeting of stockholders may be called only by our chairman of the board, chief executive officer or president, or by a resolution adopted by a majority of our board of directors.

Requirements for Advance Notification of Stockholder Nominations and Proposals—Our bylaws establish advance notice procedures with respect to stockholder proposals to be brought before a stockholder meeting and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors.

Elimination of Stockholder Action by Written Consent—Our certificate of incorporation and bylaws eliminate the right of stockholders to act by written consent without a meeting.

Staggered Board—Our board of directors is divided into three classes. The directors in each class will serve for a three-year term, one class being elected each year by our stockholders. This system of electing and removing directors may tend to discourage a third-party from making a tender offer or otherwise attempting to obtain control of us, because it generally makes it more difficult for stockholders to replace a majority of the directors.

Removal of Directors—Our certificate of incorporation provides that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two thirds of the total voting power of all of our outstanding voting stock then entitled to vote in the election of directors.

Stockholders Not Entitled to Cumulative Voting—Our certificate of incorporation does not permit stockholders to cumulate their votes in the election of directors. Accordingly, the holders of a majority of the outstanding shares of our Common Stock entitled to vote in any election of directors can elect all of the directors standing for election, if they choose, other than any directors that holders of our Preferred Stock may be entitled to elect.

Delaware Anti-Takeover Statute—We are subject to Section 203 of the Delaware General Corporation Law, which prohibits persons deemed to be "interested stockholders" from engaging in a "business combination" with a publicly held Delaware corporation for three years following the date these persons become interested stockholders unless the business combination is, or the transaction in which the person became an interested stockholder was, approved in a prescribed manner or another prescribed exception applies. Generally, an "interested stockholder" is a person who, together with affiliates and associates, owns, or within three years prior to the determination of interested stockholder status did own, 15% or more of a corporation's voting stock. Generally, a "business combination" includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. The existence of this provision may have an anti-takeover effect with respect to transactions not approved in advance by the board of directors.

Choice of Forum—Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative form, the Court of Chancery of the State of Delaware is the exclusive forum for the following types of actions or proceedings under Delaware statutory or common law: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of a fiduciary duty or other wrongdoing by any of our directors, officers, employees or agents to us or our stockholders; (3) any action asserting a claim against us arising pursuant to any provision of the General Corporation Law of the State of Delaware or our certificate of incorporation or bylaws; (4) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws; or (5) any action asserting a claim governed by the internal affairs doctrine. This provision does not apply to suits brought to enforce a duty or liability created by the Exchange Act or any other claim for which the U.S. federal courts have exclusive jurisdiction. Our certificate of incorporation also provides that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock will be deemed to have notice of and to have consented to this choice of forum provision. It is possible that a court of law could rule that the choice of forum provision contained in our certificate of incorporation is inapplicable or unenforceable if it is challenged in a proceeding or otherwise.

Amendment of Charter Provisions—The amendment of any of the above provisions, except for the provision making it possible for our board of directors to issue Preferred Stock, would require approval by holders of at least two thirds of the total voting power of all of our outstanding voting stock.

The provisions of Delaware law, our certificate of incorporation and our bylaws could have the effect of discouraging others from attempting hostile takeovers and, as a consequence, they may also inhibit temporary fluctuations in the market price of our Common Stock that often result from actual or rumored hostile takeover attempts. These provisions may also have the effect of preventing changes in the composition of our board and management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

Symbol and Listing

Our Common Stock is listed on The Nasdaq Global Market under the symbol “PTGX.”

Transfer Agent and Registrar

The transfer agent and registrar for our Common Stock is American Stock Transfer & Trust Company, LLC. The transfer agent and registrar’s address is 6201 15th Avenue, Brooklyn, New York 11219. Telephone number is (800) 937-5449.

Exhibit 21.1

SUBSIDIARIES OF PROTAGONIST THERAPEUTICS, INC.

Subsidiary	Jurisdiction of Formation/Organization
Protagonist Pty Limited	Australia

Exhibit 23.1

CONSENT OF ERNST & YOUNG LLP, INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-230213, No. 333-213120, No. 333-216532, No. 333-223500, No. 333-225294, No. 333-237066 and No. 333-254090) and in the Registration Statements on Form S-3 (No. 333-227216, No. 333-234414 and No. 333-251254) of Protagonist Therapeutics, Inc. and in the related Prospectuses, as applicable, of our reports dated February 28, 2022, with respect to the consolidated financial statements of Protagonist Therapeutics, Inc., and the effectiveness of internal control over financial reporting of Protagonist Therapeutics, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2021.

/s/ Ernst & Young LLP

Redwood City, California
February 28, 2022

Exhibit 23.2

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-254090, No. 333-237066, No. 333-230213, No. 333-213120, No. 333-216532, No. 333-223500 and No. 333-225294) and Form S-3 (No. 333-251254, No. 333-227216 and No. 333-234414) of Protagonist Therapeutics, Inc. of our report dated March 10, 2020 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
San Jose, CA
February 28, 2022

Exhibit 31.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER
Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Dinesh V. Patel, certify that:

1. I have reviewed this Annual Report on Form 10-K of Protagonist Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and we have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an Annual Report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ Dinesh V. Patel, Ph.D.

Date: February 28, 2022

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

Exhibit 31.2

CERTIFICATION OF CHIEF FINANCIAL OFFICER
Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Don Kalkofen, certify that:

1. I have reviewed this Annual Report on Form 10-K of Protagonist Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and we have:

   a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an Annual Report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ Don Kalkofen

Date: February 28, 2022

Don Kalkofen
Chief Financial Officer

Exhibit 32.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER AND CHIEF FINANCIAL OFFICER

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Dinesh V. Patel, Chief Executive Officer of Protagonist Therapeutics, Inc. (the "Company"), and Don Kalkofen, Chief Financial Officer of the Company, each hereby certify that, to the best of his knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2021 (the "Annual Report"), to which this Certification is attached as Exhibit 32.1, fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Dinesh V. Patel, Ph.D.

Date: February 28, 2022

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

/s/ Don Kalkofen

Date: February 28, 2022

Don Kalkofen
Chief Financial Officer

This certification accompanies the Form 10-K to which it relates, 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.