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, 2023

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 of registrant's principal executive offices, including zip code)	**(510) 474-0170 (Registrant's telephone number, including area code)**

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

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

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

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large Accelerated Filer	☒	Accelerated Filer	☐
Non-Accelerated Filer	☐	Smaller Reporting Company	☐
		Emerging Growth Company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

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

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

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

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant was approximately $1.6 billion as of June 30, 2023, based upon the closing sale price on The Nasdaq Stock Market LLC reported on June 30, 2023. Excludes an aggregate of 725,794 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, 2023, the registrant assumed that a stockholder was an affiliate of the registrant at June 30, 2023 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, 2023. 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 58,274,998 shares of registrant's Common Stock, par value $0.00001 per share, outstanding as of February 22, 2024.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant's definitive Proxy Statement for the registrant's 2024 Annual Meeting of Stockholders are incorporated by reference into Part III of this report. Such proxy statement will be filed with the Securities and Exchange Commission within 120 days after the end of the registrant's fiscal year ended December 31, 2023.

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

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PART I

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

Summary of Risk Factors

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

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

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

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

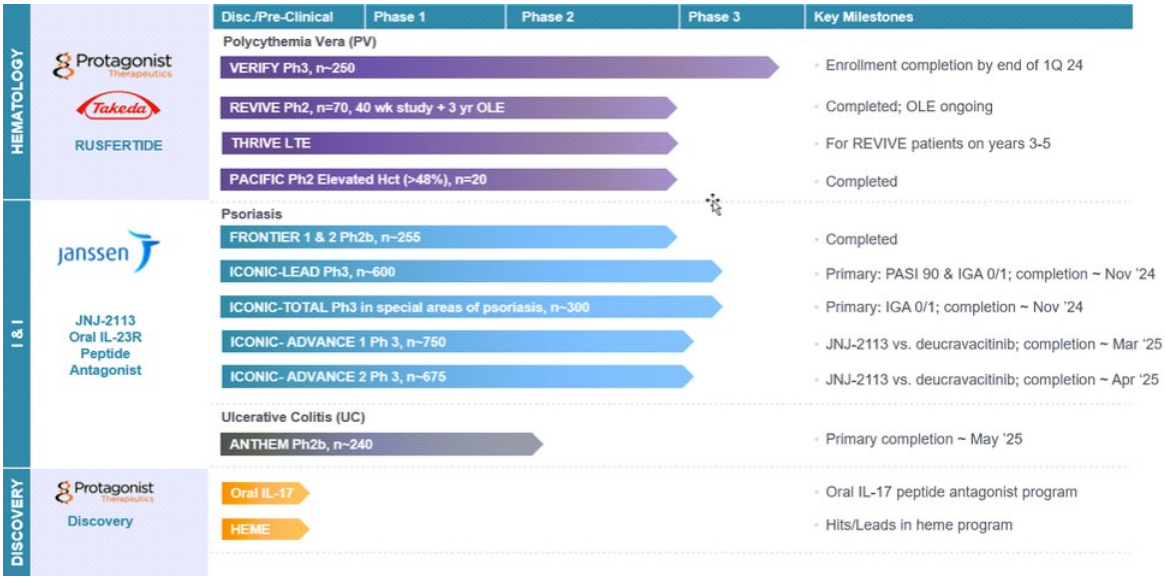
- Our stock price has been and will likely continue to be volatile and may decline, regardless of our operating performance.

Item 1. Business

OVERVIEW

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

Figure 1: Our Product Pipeline



Rusfertide

Our most advanced clinical asset, rusfertide (generic name for PTG-300), is an injectable hepcidin mimetic in development for the potential treatment of polycythemia vera ("PV") and other blood disorders. Hepcidin is a key hormone in regulating iron equilibrium and is critical to the proper development of red blood cells ("RBCs"). Rusfertide mimics the effect of the natural hormone hepcidin, but with greater potency, solubility and stability. Data from our rusfertide Phase 2 clinical trials presented at medical conferences from 2021 through 2023 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. Our rusfertide Phase 2 clinical trials include the following:

- REVIVE, a Phase 2 proof of concept ("POC") trial, was initiated in the fourth quarter of 2019. We completed enrollment of patients in the first quarter of 2022 and 70 patients were enrolled through the

end of the randomized withdrawal portion of the trial, which was completed during the first quarter of 2023 and is continuing in an ongoing open-label extension ("OLE");

- THRIVE, a Phase 2 long-term extension trial for REVIVE patients on years three through five of treatment; and

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

In March 2023, we announced positive topline results from the blinded, placebo-controlled, randomized withdrawal portion of the REVIVE trial. Subjects receiving rusfertide achieved statistically significant improvements versus placebo in the trial's primary endpoint. The double-blind, placebo-controlled, 12-week randomized withdrawal portion was included as Part 2 of the REVIVE trial to evaluate rusfertide in PV patients with frequent phlebotomy requirements. In the REVIVE trial, subjects were initially enrolled in the 28-week open label dose-titration and efficacy evaluation Part 1 of the study, followed by 1:1 randomization of 53 subjects to placebo versus rusfertide therapy for a subsequent duration of 12 weeks. More subjects receiving rusfertide during the blinded randomized withdrawal portion of the REVIVE trial were responders compared with placebo (69.2% versus 18.5%, p=0.0003). A trial subject was defined as a responder if the subject completed 12 weeks of double-blind treatment while maintaining hematocrit control without phlebotomy eligibility and without phlebotomy. During the 12 weeks of the blinded randomized withdrawal, 92.3% of subjects on rusfertide (24 out of 26) were not phlebotomized.

Data from the REVIVE trial presented at the European Hematology Association Congress in June 2023 suggested that rusfertide treatment results in highly statistically significant reduction in the need for therapeutic phlebotomy in phlebotomy-dependent patients, leading to rapid, sustained and durable control of hematocrit levels below 45%. Rusfertide was well tolerated, with localized injection site reactions ("ISRs") comprising the majority of adverse events.

Long-term follow up data from the REVIVE trial presented at the American Society of Hematology ("ASH") Annual Meeting in December 2023 showed durable hematocrit control, decreased phlebotomy use, long-term tolerability, and no new safety signals in patients with PV. An analysis of the PACIFIC Phase 2 trial was also presented that indicated rusfertide improves markers of iron deficiency in patients with PV. In addition, data was presented regarding the prevalence of thromboembolic events and secondary cancers in PV patients not treated with rusfertide. In February 2024, the full Phase 2 REVIVE trial results, including efficacy and safety data, were published in the New England Journal of Medicine.

We have initiated VERIFY, a global double-blind, placebo-controlled Phase 3 clinical trial of rusfertide in PV for approximately 250 patients. We expect enrollment completion by the end of the first quarter of 2024. By the end of 2024, we expect to receive the results of our ongoing two-year study evaluating the carcinogenicity potential of rusfertide when administered once weekly to rats.

In January 2024, we entered into a worldwide license and collaboration agreement for the development and commercialization of rusfertide with Takeda, which is yet to become effective. Under the terms of the agreement, we expect to receive an upfront payment of $300 million and to be eligible to receive additional worldwide development, regulatory and commercial milestone payments of up to $330 million, as well as tiered royalties from 10% to 17% on ex-U.S. net sales. We expect to be responsible for research and development through the completion of the Phase 3 VERIFY trial and U.S. regulatory approval. Takeda is expected to have rights for ex-U.S. development and to be responsible for leading global commercialization activities. We and Takeda expect to also share equally in U.S. profits and losses (50% to us and 50% to Takeda).

Further details related to the agreement, including our right to opt-out of the 50:50 U.S. profit and loss sharing arrangement in exchange for enhanced economics, are available in our Current Report on Form 8-K filed on January 31, 2024 with the U.S. Securities and Exchange Commission (the "SEC"). The effectiveness of the agreement is dependent on and subject to the termination or expiration of any applicable waiting periods under the Hart-Scott-Rodino Act (the "HSR Act").

JNJ-2113 (formerly PN-235)

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

In May 2017, we entered into a worldwide license and collaboration agreement with JNJ, formerly Janssen, to co-develop and co-detail our IL-23R antagonist compounds, including PTG-200 (JNJ-67864238) and certain related compounds for all indications, including inflammatory bowel disease ("IBD"). PTG-200 was a first-generation investigational, orally delivered, IL-23R antagonist for the treatment of IBD. The agreement with JNJ 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 JNJ to independently research and develop collaboration compounds for multiple indications in the IL-23 pathway and further align our financial interests.

Following completion of a Phase 1 trial in the fourth quarter of 2021, a decision was made by JNJ to advance second-generation product candidate JNJ-2113 (JNJ-77242113) based on its superior potency and overall pharmacokinetic and pharmacodynamic profile.

In February 2022, JNJ initiated FRONTIER 1, a 255-patient Phase 2b clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis, which was completed in December 2022. FRONTIER 1 was a randomized, multicenter, double-blind, placebo-controlled trial that evaluated three once-daily dosages and two twice-daily dosages of JNJ-2113 taken orally. The primary endpoint of the trial was the proportion of patients achieving PASI-75 (a 75% improvement in skin lesions as measured by the Psoriasis Area and Severity Index ("PASI")) at 16 weeks. In July 2023, we announced updated positive topline results from the trial, which were presented by JNJ at the World Congress of Dermatology in Singapore. JNJ-2113 achieved the trial's primary and secondary efficacy endpoints. A statistically significant greater proportion of patients who received JNJ-2113 achieved PASI-75 as well as PASI-90 and PASI-100 (90% and 100% improvement, respectively, in skin lesions as measured by the PASI) responses compared to placebo at week 16 in all five of the trial's treatment groups. A clear dose response was observed across an eight-fold dose range. Treatment was well tolerated, with no meaningful difference in frequency of adverse events across treatment groups versus placebo.

JNJ has initiated five additional JNJ-2113 trials, including:

- ICONIC-LEAD – A 600-patient randomized, controlled Phase 3 trial to evaluate the safety and efficacy of JNJ-2113 compared with placebo in participants with moderate-to-severe plaque psoriasis, with PASI-90 and Investigator's Global Assessment ("IGA") score of 0 (clear) or 1 (almost clear) as co-primary endpoints;

- ICONIC-TOTAL – A 300-patient randomized, controlled Phase 3 trial to evaluate the efficacy and safety of JNJ-2113 compared with placebo for the treatment of plaque psoriasis in participants with at least moderate severity affecting special areas (scalp, genital, and/or palms of the hands and soles of the feet) with overall IGA score of 0 or 1 as the primary endpoint;

- ICONIC ADVANCE 1 – A 750-patient randomized, controlled Phase 3 trial to evaluate the effectiveness of JNJ-2113 in participants with moderate-to-severe plaque psoriasis compared to placebo and Sotyktu ("deucravacitinib"). The trial's primary co-endpoints are PASI-90 and IGA score of 0 or 1;

- ICONIC ADVANCE 2 – A 675-patient Phase 3 trial similarly designed to ICONIC ADVANCE 1, which is expected to start enrolling patients later in 2024; and

- ANTHEM-UC – A 240-patient Phase 2b randomized, controlled trial to evaluate the safety and effectiveness of JNJ-2113 compared with placebo in participants with moderate-to-severely active ulcerative colitis ("UC").

All of the trials in the ICONIC program will use the once-daily, immediate release formulation of JNJ-2113 from the previously completed FRONTIER 1 study. The estimated primary completion date for the ICONIC-LEAD and ICONIC-TOTAL trials is November 2024 (see NCT06095115 and NCT06095102, respectively, at clinicaltrials.gov). The estimated primary completion dates for the ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2 trials are March 2025 and April 2025, respectively (see NCT06143878 and NCT06220604, respectively, at clinicaltrials.gov). The estimated primary completion date for the ANTHEM-UC trial is May 2025 (see NCT06049017 at clinicaltrials.gov). Other Phase 2 trials of JNJ-2113 include the SUMMIT trial for the treatment of moderate-to-severe plaque psoriasis and FRONTIER 2, a long-term extension study, both of which were completed by JNJ in 2023.

We earned a $50.0 million milestone payment upon dosing of the third patient in the ICONIC-TOTAL Phase 3 trial in late October 2023, which we received in December 2023. We earned a $10.0 million milestone payment upon the dosing of the third patient in the ANTHEM Phase 2b trial in UC in December 2023, which we received in January 2024. To date, we have earned $172.5 million in nonrefundable payments from JNJ. We remain eligible for up to approximately $795.0 million in future development and sales milestone payments, inclusive of the potential milestones listed below:

- $115.0 million milestone payment upon JNJ-2113 meeting the co-primary endpoints in any one of the four ICONIC program Phase 3 trials;
- $35.0 million milestone payment upon the filing of a New Drug Application ("NDA") for JNJ-2113 with the U.S. Food and Drug Administration (the "FDA");
- $50.0 million milestone payment upon approval of the NDA by the FDA; and
- $15.0 million milestone payment upon the advancement of JNJ-2113 into a Phase 3 trial in a second indication.

We also remain eligible to receive upward tiering royalties on net product sales at percentages ranging from six percent to ten percent, with ten percent applicable for net sales over $4.0 billion.

At JNJ's Enterprise Business Review in December 2023, JNJ highlighted JNJ-2113 as a potential first- and best-in class targeted oral IL-23 peptide antagonist with potential across multiple indications, including plaque psoriasis, psoriatic arthritis and IBD, with potential peak year sales projection of $5.0 billion plus. JNJ IL-23 monoclonal antibody ("mAb") drugs Stelara and Tremfya generated $14.0 billion in revenues in 2023.

In February 2024, the JNJ-2113 Phase 2b FRONTIER 1 trial results in adults living with moderate-to-severe plaque psoriasis were published in the New England Journal of Medicine.

PN-943

PN-943 is a wholly owned investigational orally delivered gut-restricted alpha 4 beta 7 specific integrin antagonist for IBD. We completed a Phase 2 trial of PN-943 in patients with moderate to severe UC in early 2023. We do not intend to dedicate further internal resources to clinical development or contract manufacturing activities for our PN-943 clinical program.

Discovery Platform

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

Importantly, constrained peptides can be designed to potentially alleviate the fundamental instability inherent in traditional peptides to allow different delivery forms, such as oral, subcutaneous, intravenous, and rectal. Our discovery pipeline has strategically focused on i) hematology and blood disorders and ii) I&I diseases. For example, we have a pre-clinical stage program to identify an orally active hepcidin mimetic, which we believe to be complementary to the injectable rusfertide for offering the best treatment options for PV, hereditary hemochromatosis and other potential erythropoietic and iron imbalance disorders.

In January 2024, we announced a new oral Interleukin-17 ("IL-17") peptide antagonist program targeting three IL-17 dimers (IL-17 AA, AF and FF) which may offer potential treatment options for hidradenitis suppurativa ("HS"), spondyloarthritis ("SpA"), plaque psoriasis and psoriatic arthritis. Our preliminary results showed similar or better in vitro potency than the currently approved drugs Cosentyx® and Taltz®. We expect to nominate a development candidate by the end of 2024.

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 PV.

Polycythemia Vera ("PV")

PV Overview and Market Opportunity

PV is a rare myeloproliferative neoplasm that is typically associated with a Janus Kinase ("JAK") 2 mutation. PV is primarily characterized by the overproduction of RBCs, which contributes to an elevated risk of cardiovascular and thrombotic events, such as heart attack and stroke. PV is also associated with a risk of disease progression to myelofibrosis or leukemia. 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, treatment guidelines for PV consistently emphasize the importance of controlling the patient's hematocrit (RBCs as a percentage of whole blood) below 45% to reduce thrombotic risk.

Early-stage patients are typically treated with low dose aspirin and therapeutic phlebotomy. Hydroxyurea may also be used alone or in combination with phlebotomy. At later stages, patients may receive interferons, marketed as Besrami® or Pegasus®, or ruxolitinib, a JAK inhibitor marketed as Jakafi®. Cytoreductive therapies such as hydroxyurea, interferons and ruxolitinib impact all cell lines and can have challenging side effect profiles associated with their cytoreductive mechanisms. We believe there are substantial PV patient groups that could benefit from a new non-cytoreductive therapeutic option which specifically targets RBCs. Although NCCN guidelines state that hematocrit levels should be maintained below 45% to reduce thrombotic risk, analysis of a large medical claims database indicated that 78% of treated PV patients did not maintain hematocrit control below 45%. These findings showed that current therapies do not offer adequate hematocrit control, highlighting a significant unmet need in the United States alone where patients may have an elevated risk of cardiovascular and thrombotic events.

There are approximately 100,000 diagnosed and treated patients living in the United States, with a similar number in Europe, representing an estimated market opportunity of approximately $1.0 billion to $2.0 billion. Patients are typically diagnosed between the ages of 50 and 70, and median survival is approximately 20 years. Approximately 60% of PV patients are considered to have moderate treatment burden, with treatments including frequent phlebotomy and high doses of hydroxyurea. We believe rusfertide can potentially benefit a broad spectrum of patients across the continuum of care, either as monotherapy or in combination with other cytoreductive therapies.

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 trial suggests allows for persistent control of hematocrit without causing iron deficiency. Rusfertide acts by

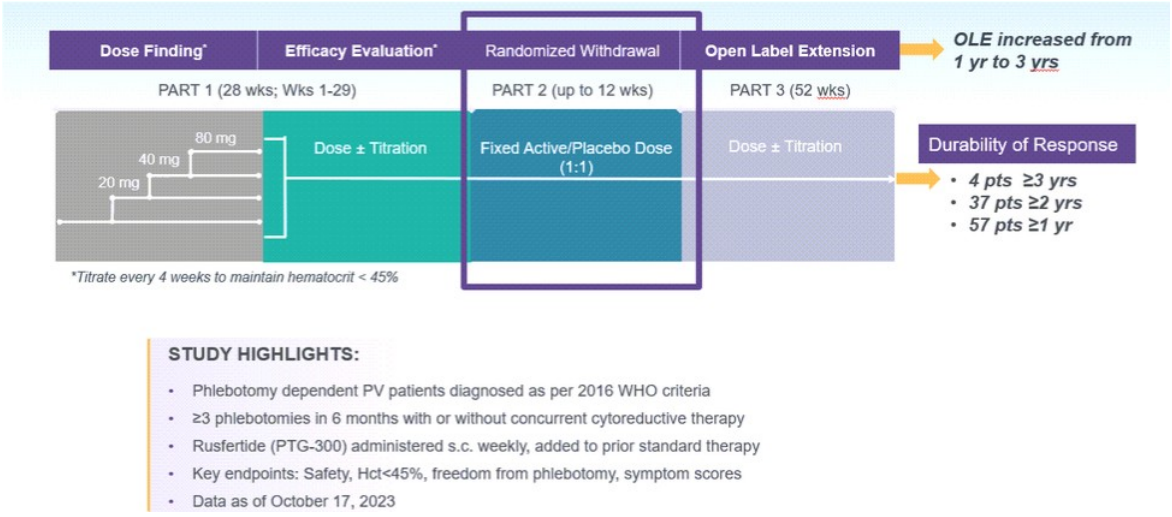
redistributing iron away from the bone marrow, where iron is essential for RBC production, thereby limiting excess RBC production while still providing sufficient iron levels to support other normal cellular and organ functions.

Cancers are common in PV patients. A retrospective analysis presented at ASH on the incidence of cancers in PV patients not treated with rusfertide demonstrated the heightened underlying cancer risk in this population, particularly among those treated with hydroxyurea. Additionally, the majority of patients with prior TEs, who are at highest risk of developing a TE, did not experience recurrent TEs while on rusfertide. The mechanisms contributing to the increased risk of cancers in PV patients are not well understood. However, the subset of PV patients treated with hydroxyurea in this study of real-world claims data had nearly twice the rate of cancers compared to phlebotomy-only treated patients.

Clinical Development of Rusfertide in PV

In the fourth quarter of 2019, we initiated REVIVE, a Phase 2 trial of rusfertide in PV designed to evaluate safety and preliminary efficacy in patients requiring phlebotomy (Figure 2). The REVIVE trial 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 trial has an OLE 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. We initiated THRIVE, a Phase 2 long-term extension trial, for REVIVE patients on years three through five of treatment.

Figure 2. REVIVE: Rusfertide Phase 2 PV Study Design



We currently have the following designations for rusfertide in PV:

- The FDA granted orphan drug designation for rusfertide for the treatment of PV in June 2020;
- The European Medicines Agency ("EMA") granted orphan drug designation for rusfertide for the treatment of PV in October 2020; and
- The FDA granted fast track designation for rusfertide for the treatment of PV in December 2020.

During the first quarter of 2021, we initiated PACIFIC, a Phase 2 trial 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. The PACIFIC trial was completed during the second quarter of 2023.

On September 16, 2021, the FDA placed a clinical hold on our then ongoing rusfertide clinical trials following our submission to the FDA of findings in a 26-week rasH2 transgenic mouse carcinogenicity study. In October 2021, we submitted a Complete Response to the FDA related to the clinical hold, and the FDA removed the clinical hold on October 8, 2021. In our Complete Response, we provided the individual patient clinical safety reports the FDA requested for human cancers observed in rusfertide clinical trials, updated the investigator brochure and patient informed consent forms for ongoing rusfertide trials, proposed new safety and stopping rules in trial protocols for our ongoing rusfertide clinical trials, and performed a comprehensive review of our rusfertide safety database. Dosing of patients and enrollment in ongoing clinical trials with rusfertide resumed in the fourth quarter of 2021. In consultation with the FDA, we implemented new safety monitoring procedures, including cancer surveillance measures (augmented dermatological examinations), and new stopping rules. Following this brief clinical hold, over 90% of patients in the REVIVE trial provided reconsent and returned to rusfertide treatment after dosing interruption and re-initiation.

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

Preliminary results indicated that rusfertide therapy resulted in rapid, sustained and durable hematocrit control without clinically meaningful changes in white blood cell and platelet counts. Subjects have been under treatment for a median of 1.5 years with the majority of subjects remaining essentially phlebotomy-free. Rusfertide demonstrated similar efficacy in all categories of patients, independent of the PV patient risk category or concurrent therapy with hydroxyurea, interferon or ruxolitinib. Trial participation was halted in one patient due to asymptomatic thrombocytosis. One patient developed acute myelogenous leukemia ("AML"), which was deemed not to be related to rusfertide. Significant adverse events included syncope, peripheral artery aneurysm, gastroenteritis, chest pain, AML, squamous cell carcinoma (skin), melanoma & basal cell carcinoma. ISRs were most common and associated with 28.1% of injections and are transient in nature.

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

In March 2023, we announced positive topline results from the blinded, placebo-controlled, randomized withdrawal portion of the REVIVE trial. Subjects receiving rusfertide achieved statistically significant improvements versus placebo in the trial's primary endpoint. The double-blind, placebo-controlled, 12-week randomized withdrawal portion was included as Part 2 of the REVIVE trial to evaluate rusfertide in PV patients with frequent phlebotomy requirements. In the REVIVE trial, subjects were initially enrolled in the 28-week open label dose-titration and efficacy evaluation Part 1 of the trial, followed by 1:1 randomization of 53 subjects to placebo versus rusfertide therapy for a subsequent duration of 12 weeks. More subjects receiving rusfertide during the blinded randomized withdrawal portion of the REVIVE trial were responders compared with placebo (69.2% versus 18.5%, p=0.0003). A trial subject was defined as a responder if the subject completed 12 weeks of double-blind treatment while maintaining hematocrit control

without phlebotomy eligibility and without phlebotomy. During the 12 weeks of the blinded randomized withdrawal, 92.3% of subjects on rusfertide (24 out of 26) were not phlebotomized.

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

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

In December 2023, we presented two-year follow up data from patients in the Phase 2 REVIVE trial who continued into the OLE at the ASH 2023 Annual Meeting. The Phase 2 trial consisted of three parts including 70 patients in the dose-finding Part 1, 59 patients in the placebo-controlled, randomized withdrawal Part 2, and 58 patients in the OLE. At the end of Part 2, 69% (18/26) of rusfertide patients achieved hematocrit control and remained phlebotomy free at 12 weeks, compared to only 19% (5/27) on placebo (p=0.0003). Among the 58 patients that continued into the OLE, as of October 17, 2023 (data cut-off date for the ASH presentation), 57 had been treated for over one year and 37 had been treated for over two years. The median follow-up was 2.1 years and data were provided out to 2.5 years in 21 patients.

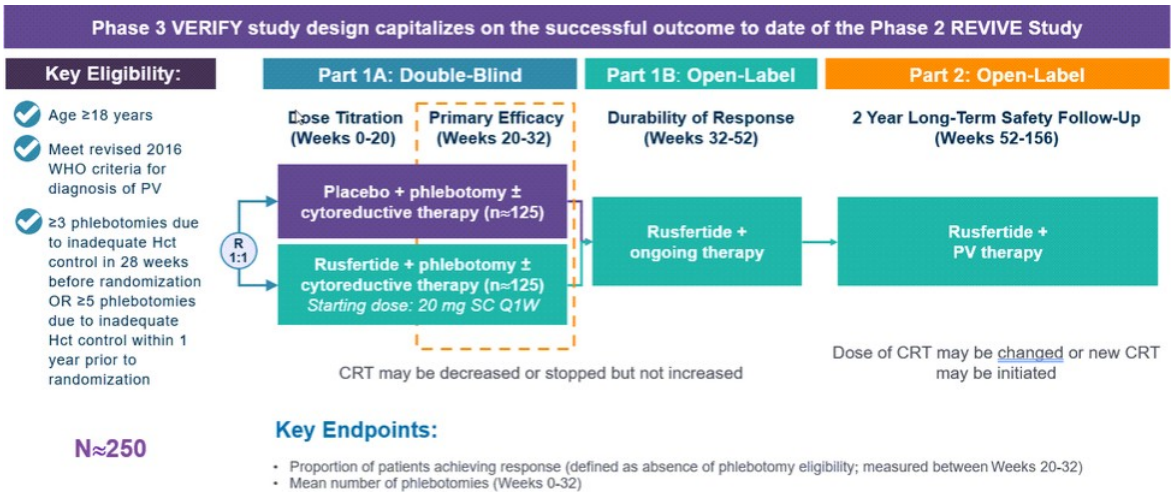
Results showed that rusfertide, when used in patients previously treated with phlebotomy with or without cytoreductive therapy through two years, resulted in:

- long-term durable control of hematocrit well below the 45% threshold, decreased red blood cell counts and decreased phlebotomy use;
- improved and normalized serum ferritin levels; and
- no new safety signals, with the majority of adverse events being grade 1-2 ISRs that decreased in frequency over time, or adverse events consistent with comorbidities anticipated in the PV population.

In February 2024, the full Phase 2 REVIVE trial results, including efficacy and safety data, were published in the New England Journal of Medicine.

We initiated VERIFY, a global double-blind, placebo-controlled Phase 3 clinical trial of rusfertide in PV for approximately 250 patients, in the first quarter of 2022 (Figure 3). We expect enrollment completion by the end of the first quarter of 2024. By the end of 2024, we expect to receive the results of our ongoing two-year study evaluating the carcinogenicity potential of rusfertide when administered once weekly to rats.

Figure 3. VERIFY: Rusfertide Phase 3 PV Study Design



In January 2024, we entered into a worldwide license and collaboration agreement for the development and commercialization of rusfertide with Takeda, which is yet to become effective. Under the terms of the agreement, we expect to receive an upfront payment of $300 million and to be eligible to receive additional worldwide development, regulatory and commercial milestone payments of up to $330 million, as well as tiered royalties from 10% to 17% on ex-U.S. net sales. We expect to be responsible for research and development through the completion of the Phase 3 VERIFY trial and U.S. regulatory approval. Takeda is expected to have rights for ex-U.S. development and to be responsible for leading global commercialization activities. We and Takeda expect to also share equally in U.S. profits and losses (50% to us and 50% to Takeda).

Further details related to the agreement, including our right to opt-out of the 50:50 U.S. profit and loss sharing arrangement in exchange for enhanced economics, are available in our Current Report on Form 8-K filed on January 31, 2024 with the SEC. The effectiveness of the agreement is dependent on and subject to the termination or expiration of any applicable waiting periods under the HSR Act.

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

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

Psoriasis

Psoriasis is a chronic inflammatory disease of the skin that affects 130 million people worldwide and 8 million in the United States, translating to 2-3% of the adult population. Psoriasis is associated with several comorbid conditions

including cardiovascular disease and obesity, and 30% of psoriasis patients develop arthritic complications. Psoriasis is also associated with significantly decreased quality of life for patients.

Plaque psoriasis is the most common form of psoriasis, which is recognized as the most prevalent immune-mediated inflammatory disease, involving skin and joints and associated with abnormalities of other systems. Several factors, such as surface area covered and symptom burden, impact whether one's psoriasis is considered mild, moderate, or severe. Typically, 3-10% of affected body surface area is considered moderate psoriasis, and more than 10% is considered severe psoriasis. Global market sales for psoriasis therapies in 2022 were $23.1 billion, with U.S. market sales of $16.3 billion. The global market forecast for 2030 anticipates sales of $30.0 billion, with U.S. market sales of $20.7 billion. Identification of the IL-23/IL-17 axis as the key pathway driving psoriatic inflammation has led to the development of more effective and safer systemic therapies that inhibit IL-17 (e.g., Taltz®, Cosentyx®) and IL-23 (e.g., Tremfya®, Skyrizi®). These biologics have revolutionized the treatment of moderate-to-severe psoriasis, with superior efficacy and safety compared to conventional oral therapies (e.g., methotrexate, cyclosporin), and first-generation biologics (e.g., anti-TNFs, Stelara®). The anti-IL-17 and anti-IL-23 classes are associated with PASI 75 scores (75% improvement in skin inflammation) in 90% of patients, and complete clearance of the skin (PASI 100) in 30-40% of patients. The anti-IL-17 class is ineffective in IBD, surprisingly showing overall worsening of disease in Phase 2 trials, which is reflected in the product labels. There is still an unmet need for new therapies. Only 25% of biologic eligible moderate-to-severe psoriasis patients are treated with a biologic. The parenteral route of administration for these advanced biologics poses a patient level barrier to entry. Two oral medicines have been approved in moderate-to-severe psoriasis. Otezla® was approved in 2014. It is the least effective of all drugs approved since 2004 with PASI 75 of approximately 30% but is used widely because of a perceived positive safety profile. In 2022, the first TYK2 inhibitor, Sotyktu®, was approved. In Phase 3 trials, it has demonstrated approximately 55% PASI 75 scores. A second TYK2 inhibitor, TAK-279 is in Phase 3 trials for moderate-to-severe plaque psoriasis. We believe there is still significant need for safe and effective oral therapies in moderate-to-severe psoriasis.

Psoriatic Arthritis

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

Inflammatory Bowel Disease ("IBD")

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

According to the Crohn's & Colitis Foundation, IBD is diagnosed in nearly 1 in 100 Americans, resulting in a population of approximately 2.4 million patients in the United States. In 2022, global sales for UC therapies were approximately $7.7 billion, and the market is expected to grow to $10.6 billion by 2028. In 2022, global sales for CD therapies were estimated to be $16.2 billion, with anticipated growth to $18.9 billion by 2028.

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's Entyvio®, which targets the α4β7 integrin pathway. Takeda reported 2022 sales of Entyvio® of approximately $6.4 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) were $10.9 billion in 2023. Three anti-IL-23 mAbs are in Phase 3 trials or beyond in IBD: Tremfya®, Skyrizi® and Ely Lilly and Company's mirikizumab. The development of oral medicine has been an unmet need and priority in IBD. The pan-JAK inhibitor Xeljanz® was approved in UC (but not CD) in 2018. The label contains black box warnings for "an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death." The more selective JAK1/3 inhibitor Rinvoq® was approved in 2022 for UC and CD. The label carries the same black box warnings. The S1P1 modulator class of oral small molecules has also demonstrated efficacy in IBD, with Zeposia® approved in UC (but not CD) in 2021, and etrasimod approved in UC in 2023. The S1P1 class is associated with immunosuppression, cardiac, pulmonary and ocular toxicities.

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

JNJ-2113: AN ORAL IL-23 RECEPTOR ANTAGONIST

JNJ License and Collaboration Agreement

We have a worldwide license and collaboration agreement with JNJ to research, develop and co-detail our IL-23 receptor ("IL-23R") antagonist compounds for all indications, including IBD. The agreement with JNJ 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 JNJ to independently research and develop collaboration compounds for multiple indications in the IL-23 pathway and further align our financial interests. See Part II, Item 7. "Management's Discussion and Analysis – Overview" and Note 3 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information. JNJ is an experienced innovator in therapeutics targeting the IL-23 pathway. Stelara® is a monoclonal antibody targeting IL-12 and IL-23 through their common p40 subunit is approved in psoriasis, psoriatic arthritis, CD and UC. Stelara® generated $10.9 billion in sales in 2023. Tremfya® is a specific IL-23 monoclonal antibody. It is approved in psoriasis and psoriatic arthritis and has completed successful Phase 3 trials in UC and CD. Tremfya® generated $3.1 billion in sales in 2023. We believe that in both psoriasis and IBD, there is an urgent need for safe and effective oral therapies. It is notable that Stelara® lost patent exclusivity in 2023 with biosimilar competition expected.

JNJ-2113 (formerly known as PN-235), an orally delivered IL-23R specific antagonist for the potential treatment of psoriasis, psoriatic arthritis and IBD indications, was discovered through our peptide technology platform. IL-23, a member of the IL-12 family of pro-inflammatory cytokines, is a protein that regulates inflammatory and immune function and plays a key role in the development of IBD. By blocking IL-23R, we believe JNJ-2113 may improve disease symptoms while potentially minimizing the risk of systemic side effects. During the fourth quarter of 2021, a decision was made by JNJ to advance development of our IL-23R antagonist JNJ-2113. For JNJ-2113, JNJ is primarily responsible for the conduct of all further development, and we were primarily responsible for the discovery, IND-enabling studies and the initial Phase 1 study.

Clinical Development of JNJ-2113

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

In February 2022, JNJ initiated FRONTIER 1, a 255-patient Phase 2b clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis, which was completed in December 2022. FRONTIER 1 was a randomized, multicenter, double-blind, placebo-controlled trial that evaluated three once-daily dosages and two twice-daily dosages of JNJ-2113 taken orally. The primary endpoint of the trial was the proportion of patients achieving PASI-75 at 16 weeks. In July 2023, we announced updated positive topline results from the trial, which were presented by JNJ at the World Congress of Dermatology in Singapore. JNJ-2113 achieved the trial's primary and secondary efficacy endpoints. A statistically significant greater proportion of patients who received JNJ-2113 achieving PASI-75 responses as well as PASI-90 and PASI-100 responses compared to placebo at week 16 in all five of the trial's treatment groups. A clear dose response was observed across an eight-fold dose range. Treatment was well tolerated, with no meaningful difference in frequency of adverse events across treatment groups versus placebo.

JNJ has initiated five additional JNJ-2113 trials, including:

- ICONIC-LEAD – A 600-patient randomized, controlled Phase 3 trial to evaluate the safety and efficacy of JNJ-2113 compared with placebo in participants with moderate-to-severe plaque psoriasis, with PASI-90 and IGA score of 0 (clear) or 1 (almost clear) as co-primary endpoints;

- ICONIC-TOTAL – A 300-patient randomized, controlled Phase 3 trial to evaluate the efficacy and safety of JNJ-2113 compared with placebo for the treatment of plaque psoriasis in participants with at least moderate severity affecting special areas (scalp, genital, and/or palms of the hands and soles of the feet) with overall IGA score of 0 or 1 as the primary endpoint;

- ICONIC ADVANCE 1 – A 750-patient randomized, controlled Phase 3 trial to evaluate the effectiveness of JNJ-2113 in participants with moderate-to-severe plaque psoriasis compared to placebo and Sotyktu ("deucravacitinib"). The trial's primary co-endpoints are PASI-90 and IGA score of 0 or 1;

- ICONIC ADVANCE 2 – A 675-patient Phase 3 trial similarly designed to ICONIC ADVANCE 1, which is expected to start enrolling patients later in 2024; and

- ANTHEM-UC – A 240-patient Phase 2b randomized, controlled trial to evaluate the safety and effectiveness of JNJ-2113 compared with placebo in participants with moderate-to-severely active UC.

All of the trials in the ICONIC program will use the once-daily, immediate release formulation from the previously completed FRONTIER 1 study. The estimated primary completion date for the ICONIC-LEAD and ICONIC-TOTAL trials is November 2024 (see NCT06095115 and NCT06095102, respectively, at clinicaltrials.gov). The estimated primary completion dates for the ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2 trials are March 2025 and April 2025, respectively (see NCT06143878 and NCT06220604, respectively, at clinicaltrials.gov). The estimated primary completion date for the ANTHEM-UC trial is May 2025 (see NCT06049017 at clinicaltrials.gov). Other Phase 2 trials of JNJ-2113 include the SUMMIT trial of JNJ-2113 for the treatment of moderate-to-severe plaque psoriasis, and FRONTIER 2, a long-term extension study, both of which were completed by JNJ in 2023.

At JNJ's Innovative Medicines Enterprise Business Review in December 2023, JNJ highlighted JNJ-2113 as a potential first- and best-in class targeted oral IL-23 peptide antagonist with potential across multiple indications, including psoriasis, psoriatic arthritis and IBD, with potential peak year sales projection of $5.0 billion plus. JNJ IL-23 mAb drugs Stelara and Tremfya generated $14.0 billion in revenues in 2023.

In February 2024, the JNJ-2113 Phase 2b FRONTIER 1 trial results in adults living with moderate-to-severe plaque psoriasis were published in the New England Journal of Medicine.

OUR PEPTIDE TECHNOLOGY PLATFORM

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

The platform is used to develop potential drug candidates (agonists and antagonists): (i) using the structure of a target, when available, (ii) *de novo* when no target structure exists, or (iii) from publicly disclosed peptide starting points. In a structure-based approach, our proprietary molecular design software and structural database of several thousand constrained peptides, termed Vectrix™, are screened to identify suitable scaffolds. The scaffolds identified form the basis of designing and constructing the first set of phage or chemical libraries. The initial hits are identified by either panning or screening such libraries, respectively. When structural information is unavailable for a target, hits are identified by panning a set of 34 proprietary cluster-based phage libraries consisting of millions of constrained peptides. Once the hits are identified, they are optimized using a set of peptide, peptide mimetic and medicinal chemistry techniques that include the incorporation of new or manipulation of existing cyclization-constraints, as well as natural or unnatural amino acids and chemical conjugation or acylation techniques. These techniques are applied to optimize potency, selectivity, stability, exposure and ultimately efficacy. For rusfertide, hit discovery and optimization relied exclusively on medicinal and computational chemistry, with no phage display, to develop potent and selective injectable candidates with enhanced stability and exposure in blood. For injectable products, stability in blood is determined using *in vitro* assay techniques to identify chemical and biological sites of degradation, which are then optimized while still maintaining potency and selectivity. Conjugation strategies are used to optimize the exposure of the injected peptide. For JNJ-2113, phage display is tightly coupled to medicinal chemistry, structural biology and oral stability techniques to develop potent, selective and orally delivered molecules. Oral stability is profiled in a series of *in vitro* and *ex vivo* assays that portray the chemical and metabolic barriers a peptide will encounter as it transits the GI and systemic compartments as needed. These metabolically labile spots in the peptides are optimized using medicinal chemistry-based approaches to engineer oral stability while maintaining selectivity and potency. Various *in vivo* pharmacology tools are then used to quantify peptide exposure in relevant GI and systemic compartments. 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 POC 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 I&I, metabolic and blood disorders and expand our technology platform to provide potential opportunities to pursue a wider variety of diseases that may include oral, topical and systemic approaches. We also intend to progress our platform to achieve systemic bioavailability and activity with oral peptides, macrocycles and peptidomimetics, thereby enabling us to address systemic diseases. Examples of this approach are our pre-clinical stage program to identify an orally active hepcidin mimetic, as was reported at the American Society for Hematology's virtual annual meeting in December 2020, the discovery and development of JNJ-2113, our IL-23R antagonist in collaboration with JNJ, and our recently announced IL-17 peptide antagonist program as described above.

Competition

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

Rusfertide

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

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

JNJ-2113

In psoriasis and psoriatic arthritis, competition will come from companies with approved injectable agents in the IL-17 and IL-12/23 pathway, including Cosentyx®, Taltz®, Siliq®, Tremfya®, and Skyrizi®. Bimekizumab (anti-IL-17A and F, UCB) has completed a positive Phase 3 program in psoriasis. Otezla® (Amgen) was the first oral agent approved in both psoriasis and psoriatic arthritis. The oral JAK inhibitors Xeljanz® (Pfizer) and Rinvoq® are approved in psoriatic arthritis. Several oral small molecules that inhibit the Janus kinase TYK2 are advancing in development. The Bristol Myers Squibb ("BMS") TYK2 inhibitor, Sotyktu®, was approved for psoriasis in 2022. Second generation allosteric TYK2 inhibitors from Nimbus Therapeutics (recently in-licensed by Takeda) are moving into Phase 3 development, and a molecule from Ventyx Biosciences has initiated Phase 2 development. Several small molecules that inhibit IL-17 have completed Phase 1 development.

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

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

- JAK inhibitors: The pan-JAK tofacitinib (Xeljanz®) is approved in UC. The next-generation selective JAK1/3 inhibitors, including Abbvie's upadacitinib (Rinvoq®) was approved in UC and

CD in 2022. Pfizer's selective JAK1/TEC inhibitor ritlecitinib is in Phase 2 development for UC and CD; and

- S1P1 receptor modulators: BMS's 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, which is progressing in Phase 2 development in UC. Other oral small molecules targeting α4β7 from Gilead and EA Pharma are in early clinical development. Many other agents are in early-stage development in IBD, including injectable anti-TLIA antibodies by Pfizer and Prometheus, which have both recently presented positive Phase 2 results in UC.

IL-17

In competitive areas, we believe there is a strong need for a differentiated oral approach. The injectable mAbs Cosentyx and Taltz targeting IL-17 AA and AF are approved in psoriasis, psoriatic arthritis, and SpA. Cosentyx was also recently the first IL-17 inhibitor approved in HS. Siliq, a mAb to the IL-17 receptor, is approved in psoriasis only and carries a black box warning for suicidal ideations. Bimzelx is a mAb that targets IL-17 AA, AF and FF. It is approved in psoriasis and psoriatic arthritis with positive phase 3 results in SpA and HS. Sonelokimab (MoonLake) is an injectable nanobody with IL-17 AA, AF and FF activity and has demonstrated POC in Phase 2 in psoriasis, psoriatic arthritis, and HS. There are several oral IL-17 small molecules in clinical development with the most advanced, DC-806 (Lilly via acquisition of DICE Therapeutics) in a Phase 2b trial in psoriasis. JNJ and Sanofi are also developing small molecules.

Material Agreements

JNJ License and Collaboration Agreement

On July 27, 2021, we entered into an Amended and Restated License and Collaboration Agreement (the "Restated Agreement") with JNJ, which amended and restated the License and Collaboration Agreement, effective July 13, 2017, by and between us and JNJ (the "Original Agreement"), as amended by the first amendment, effective May 7, 2019 (the "First Amendment"). Upon the effectiveness of the Original Agreement, we received a non-refundable, upfront cash payment of $50.0 million from JNJ. Upon the effectiveness of the First Amendment, we received a $25.0 million payment from JNJ in 2019. In the first quarter of 2020, we received a $5.0 million payment triggered by the successful nomination of a second-generation IL-23R antagonist development compound. In the fourth quarter of 2021, we received a $7.5 million milestone payment from JNJ triggered by completion of the data collection for JNJ-2113 Phase 1 activities. In the second quarter of 2022, we received a $25.0 million milestone payment in connection with the dosing of the third patient in FRONTIER 1 during the first quarter of 2022. In the fourth quarter of 2023, we received a $50.0 million milestone payment in connection with the dosing of the third patient in the ICONIC-TOTAL Phase 3 trial. In the first quarter of 2024, we received a $10.0 million milestone payment in connection with the dosing of the third patient in the ANTHEM Phase 2b trial during the fourth quarter of 2023. See Part II, Item 7, "Management's Discussion and Analysis – Overview" and Note 3 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Takeda Collaboration Agreement

In January 2024, we entered into a worldwide license and collaboration agreement for the development and commercialization of rusfertide with Takeda (the "Takeda Collaboration Agreement"), which is yet to become effective. See Note 15 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Research Collaboration and License Agreement with Zealand Pharma A/S

In June 2012, we entered into a Research Collaboration and License Agreement (the "Zealand Agreement") with Zealand Pharma A/S ("Zealand") to identify, optimize and develop novel disulfide-rich peptides to discover a hepcidin mimetic. We amended this agreement on February 28, 2014, at which point Protagonist assumed responsibility for the development program. See Part II, Item 7. "Management's Discussion and Analysis – Contractual Obligations and Other Commitments" and Note 7 and Note 9 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 26 issued U.S. patents, over 62 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 mimetics peptides, as well as methods of synthesizing and using these peptides to treat 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. 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 studies and clinical trials and eventually for commercial supplies and intend to continue to do so in the future. We do not own or operate any manufacturing facilities and we have no plans to build any owned clinical or commercial scale manufacturing capabilities. We believe that the use of contract manufacturing organizations ("CMOs") eliminates the need for us to directly invest in manufacturing facilities, equipment and additional staff. We have established a global supply chain for raw material, active pharmaceutical ingredients ("API"), drug product manufacturing and distribution. We work with contract manufacturers in the United States, Europe and Asia. Although we rely on contract manufacturers, our personnel and consultants have extensive manufacturing and quality control experience overseeing CMOs. We regularly consider second source or back-up manufacturers for both API and drug product manufacturing. To date, our third-party manufacturers have met the manufacturing requirements for our product candidates. We expect third-party manufacturers to be capable of providing supplies needed for our product candidates to meet anticipated full-scale commercial demands, and we have selected CMOs that can manufacture our product candidates for our ongoing and planned clinical trials as well as commercial supplies. We currently engage CMOs on a "fee for services" basis for our current development and clinical supplies.

Government Regulation

The FDA and comparable regulatory authorities in state and local jurisdictions and in other countries impose substantial requirements upon companies involved in the clinical development, manufacture, marketing and distribution

of drugs, such as those we are developing. These agencies and other federal, state and local entities regulate, among other things, the research and development, testing, manufacture, quality control, safety, effectiveness, labeling, storage, record keeping, approval, advertising and promotion, distribution, post-approval monitoring and reporting, sampling and export and import of our product candidates.

U.S. Government Regulation

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

Pre-clinical Studies

Pre-clinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. These pre-clinical studies must comply with GLP. An IND sponsor must submit the results of the pre-clinical tests, together with manufacturing information, analytical data and any available clinical data or literature to the FDA as part of an IND. Some pre-clinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or

questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

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

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

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

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

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

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

Marketing Approval

Following successful completion of the required clinical testing and the results of the pre-clinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other information, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to an application user fee. Under the Prescription Drug User Fee Act ("PDUFA") guidelines, the FDA has a target of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes twelve months from the date the NDA is submitted to the FDA.

In addition, under the Pediatric Research Equity Act of 2003, certain NDAs or supplements to an NDA must contain data that is adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements.

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

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

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

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

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

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

Fast Track Designation

The FDA has various programs, such as fast track designation. These programs are intended to expedite or simplify the process for the development and FDA review of drugs for the treatment of serious or life-threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients faster. The sponsor of a new drug may request fast track designation concurrent with, or after, the filing of the IND. To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life threatening disease or condition and demonstrates the potential to address an unmet medical need. A product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or

safety. Fast track designation provides additional opportunities for interaction with the FDA's review team and may allow for rolling review of NDA components before the completed application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA. However, the FDA's time goal for reviewing an application does not begin until the last section of the NDA is submitted. The FDA may decide to rescind the fast track designation if it determines that the qualifying criteria no longer apply.

Orphan Designation

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

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

There is some uncertainty with respect to the FDA's interpretation of the scope of orphan drug exclusivity. Historically, exclusivity was specific to the orphan indication for which the drug or biologic was approved. As a result, the scope of exclusivity was interpreted as preventing approval of a competing product. However, in 2021, the federal court in Catalyst Pharmaceuticals, Inc. v. Becerra, suggested that orphan drug exclusivity covers the full scope of the orphan-designated "disease or condition" regardless of whether a drug obtained approval for a narrower use.

Breakthrough Therapy Designation

A sponsor can request designation of a drug candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are also eligible for accelerated approval and priority review. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy. The FDA may decide to rescind the breakthrough designation if it determines that the qualifying criteria no longer apply.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA. These regulations include requirements relating to recordkeeping, periodic reporting, product sampling and

distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to FDA review and approval. There also are continuing, annual program user fee requirements for any marketed products.

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

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

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

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

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

Coverage and Reimbursement

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

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

In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our product candidates or a decision by a third-party payor to not cover our product candidates could reduce physician usage of our products candidates, once approved, and have a material adverse effect on our sales.

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

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

Further, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. This scrutiny has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the Trump administration implemented drug pricing reform through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that attempt to implement several of the administration’s proposals The FDA also released a final rule, effective November 30, 2020, implementing a portion of the importation executive order providing guidance for states to build and submit importation plans for drugs from

Canada. Further, on November 20, 2020, the U.S. Department of Health and Human Services ("HHS") finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule was delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers.

Federal and state legislatures have become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare therapies.

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

Other Health Care Laws and Compliance Requirements

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

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

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

Government Regulation Outside of the United States

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

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

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

Under the CTR, a sponsor may submit a single application for approval of a clinical trial through a centralized EU clinical trials portal. One national regulatory authority (the reporting EU Member State proposed by the applicant) will take the lead in validating and evaluating the application consult and coordinate with the other concerned Member States. If an application is rejected, it may be amended and resubmitted through the EU clinical trials portal. If an approval is issued, the sponsor may start the clinical trial in all concerned Member States. However, a concerned EU Member State may in limited circumstances declare an "opt-out" from an approval and prevent the clinical trial from being conducted in such Member State. The CTR also aims to streamline and simplify the rules on safety reporting and introduces enhanced transparency requirements such as mandatory submission of a summary of the clinical trial results to the EU Database ("CTIS"). Since January 31, 2023, submission of initial clinical trial applications via CTIS is mandatory, and by January 31, 2025, all ongoing trials approved under the former Clinical Trials Directive will need to comply with the CTR and have to be transitioned to CTIS.

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

Drug Marketing Authorization

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

The centralized procedure provides for the grant of a single MA that is issued by the European Commission ("EC") following the scientific assessment of the application by the EMA that is valid for all EU Member States as well as in the three additional EEA Member States. The centralized procedure is compulsory for specific medicinal products, including for medicines developed by means of certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products and medicinal products with a new active substance indicated for the treatment of certain diseases (AIDS, cancer, neurodegenerative disorders, diabetes, autoimmune and viral diseases). For medicinal products containing a new active substance not yet authorized in the EEA before May 20, 2004

and indicated for the treatment of other diseases, medicinal products that constitute significant therapeutic, scientific or technical innovations or for which the grant of an MA through the centralized procedure would be in the interest of public health at EU level, an applicant may voluntarily submit an application for an MA through the centralized procedure.

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

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

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

All new MAAs must include a Risk Management Plan ("RMP"), describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available. The regulatory authorities may also impose specific obligations as a condition of the MA.

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

European Data Protection Laws

The collection and use of personal health data and other personal data in the EU is governed by the provisions of the European General Data Protection Regulation (EU) 2016/679 ("GDPR"). The GDPR imposes strict requirements on

the processing of personal data, including the legal basis for the processing, the information that has to be provided to individuals before their data is processed, notification obligations to national data protection authorities, and the technical and organization measures to ensure the security and confidentiality of the personal data. EU Member States may also have additional requirements for health, genetic, and biometric data through their national legislation. The GDPR also imposes restrictions on the transfer of personal data to countries outside of the EU that do not provide an adequate level of data protection. To enable such transfers, appropriate safeguards, such as standard contractual clauses must be in place. Alternatively, such transfers can be based on an adequacy decision by the EU commission. Regarding transfers to the US, the EU commission issued an adequacy decision for transfers to companies that are certified under the new EU-US Data Privacy Framework, which entered into force on June 10, 2023.

Environmental, Social, Governance ("ESG") and Human Capital Disclosures

Governance and Leadership

Our Board of Directors ("Board") plays a pivotal role in overseeing our strategic direction, risk management related to ESG matters and our overall governance framework. Our Board composition reflects a diversity in backgrounds, skills and experiences. Our executive leadership team is responsible for driving our performance and guiding our long-term growth initiatives. We believe in fostering a culture of integrity, ethical decision making, and responsible corporate citizenship.

Business Ethics

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

Environmental Commitment

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

Social Responsibility

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

Human Capital

We recognize that our success is driven by the knowledge, skills and dedication of our employees. Our human capital is fundamental to our ability to innovate and develop life-changing peptide drug therapies. We invest in our employees by seeking to foster a supportive, diverse and inclusive workplace. We offer competitive compensation and benefits and provide opportunities for professional growth and development.

As of December 31, 2023, our total global workforce consisted of 112 full-time equivalent employees, 85 of whom were in research and development. The remaining 27 employees worked in finance, legal, business development, human resources and administrative support. 104 of our full-time equivalent employees are located in the United States and 8 are located in Australia. None of our employees are represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good. We track and report internally on key talent metrics including workforce demographics, diversity data and the status of open positions. We are committed to equality, inclusion and diversity in the workplace. As of December 31, 2023, approximately 70% of our workforce identify as members of underrepresented ethnic communities and over 50% identify as female. We strive to interview diverse candidates for our open positions to promote inclusion and equal employment opportunities.

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 have robust recruitment and retention processes in place that are designed to attract and retain individuals who possess the necessary expertise, innovative drive and commitment to contribute to our mission. We offer competitive compensation packages, including performance-based incentives, equity awards, and comprehensive benefits, including 401(k) plan matching contributions and an employee stock purchase plan for U.S. employees. 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 U.S. employees' monthly healthcare premiums. For the year ended December 31, 2023, our employee turnover rate was approximately 7%.

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 from 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. We invest in initiatives aimed at promoting employee well-being. To support our employees personally and professionally, we have Employee Assistance Programs to address employee challenges and needs. We value feedback from our employees and use it to improve our workplace policies and practices.

Corporate and Other Information

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

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

Item 1A. Risk Factors

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

Risks Related to Clinical Development

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

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

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

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

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

Our product candidates require additional clinical development, regulatory approval and secure sources of commercial manufacturing supply prior to commercialization. We cannot assure you that our clinical trials for our product candidates will be initiated or completed in a timely manner or successfully, or at all. Further we cannot be certain that we plan to advance any other product candidates into clinical trials. Moreover, any delay or setback in the development of any product candidate would be expected to adversely affect our business and cause our stock price to fall. For example, our stock price dropped significantly in September 2021 following the announcement of a full clinical hold imposed by the FDA on our rusfertide clinical studies. Our stock price also dropped significantly in April 2022 following the announcement of our voluntary withdrawal of Breakthrough Therapy Designation for rusfertide and the announcement of topline data from our Phase 2 clinical trial evaluating PN-943 in UC.

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

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

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

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

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

In addition, there are a significant number of global clinical trials in hematologic disorders that are currently ongoing, especially in Phases 2 and 3, making it highly competitive and challenging to recruit subjects. Other companies targeting the same patient populations as our clinical trials for such medicines may make it more difficult for us to complete enrollment in our clinical trials. Furthermore, any negative results we may report in clinical trials of our product candidate may make it difficult or impossible to recruit and retain patients in other ongoing or subsequent clinical trials of that same product candidate. Delays or failures in planned patient enrollment or retention may result in increased costs, program delays or both. In addition, we are subject to risks and uncertainties as a result of the ongoing military conflict in Ukraine and Russia. For example, in 2022 we closed down clinical trial sites in Russia and Ukraine at which a limited number of subjects were enrolled in our PN-943 Phase 2 IDEAL trial.

If we experience material delays in the completion of any clinical trial, the reduction in remaining patent term would harm the commercial prospects for that product candidate and our ability to generate product revenue from any of

these product candidates will be delayed. Any of these occurrences may harm our business, financial condition and prospects significantly.

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

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

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

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

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

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

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

We have focused our limited resources to pursue particular product candidates and indications, and consequently, we may fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we have historically focused on research programs and product candidates mainly on the development of rusfertide, the product candidates subject to our JNJ collaboration and, through early 2022, PN-943. Going forward, we have no plans to devote further resources to PN-943 as part of our ongoing commitment to optimize and focus resources toward our rusfertide program in PV. In addition, in keeping with

our organizational prioritization of rusfertide in PV, plans to initiate trials of rusfertide in additional disease indications have been paused. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration partnerships, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Risks Related to our Financial Position and Capital Requirements

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

We have incurred significant operating losses every year since inception and expect to continue to incur operating losses for the foreseeable future. As of December 31, 2023, we had an accumulated deficit of $615.7 million. We expect to continue to incur significant research, development and other expenses related to our ongoing operations and product development. As a result, we expect to continue to incur losses in the future as we continue our development of, and seek regulatory approvals for, our product candidates.

We do not anticipate generating revenue from sales of products for a number of years, if ever, and we have not yet successfully completed registrational or pivotal clinical trials for our product candidates. If any of our product candidates fail in clinical trials or do not gain regulatory approval or fail to achieve market acceptance, we may never become profitable. Revenue we generate from our collaborations with JNJ, Takeda, 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 may require 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 may require additional future capital in order to complete clinical development and, if we are successful, to commercialize any of our current product candidates. Further, in the event that the Restated Agreement with JNJ or the Takeda Collaboration Agreement is terminated, we may not receive any additional fees or milestone payments under that agreement. Absent the funding support obtained under the Restated Agreement or the Takeda Collaboration 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, 2023, we had cash, cash equivalents and marketable securities of $341.6 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 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 have in the past and may in the future seek additional funding through a combination of equity offerings, including the use of the 2022 ATM facility, debt financings, collaborations and/or licensing arrangements. Additional funding may not be available to us on acceptable terms, or at all. Our ability to raise additional capital may be adversely impacted by adverse economic conditions and market volatility. The incurrence of indebtedness and/or the issuance of certain equity securities could result in fixed payment obligations and could also result in certain additional restrictive covenants, such as limitations on our ability to incur debt and/or issue additional equity, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. In addition, the issuance of additional equity securities by us, or the possibility of such issuance,

may cause the market price of our common stock to decline. In the event that we enter into additional collaborations and/or licensing arrangements in order to raise capital, we may be required to accept unfavorable terms, including relinquishing or licensing to a third party on unfavorable terms our rights to our proprietary technology platform or product candidates. To the extent that we raise additional capital through the sale of equity securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. If we issue common stock or securities convertible into common stock, our common stockholders will experience additional dilution and, as a result, our stock price may decline.

Risks Related to our Reliance on Third Parties

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

JNJ-2113, the product candidate in development pursuant to our JNJ collaboration, may prove to have undesirable or unintended side effects or other characteristics adversely affecting its safety, efficacy or cost effectiveness that could prevent or limit its approval for marketing and successful commercial use, or that could delay or prevent the commencement and/or completion of clinical trials. Under the terms of the Restated Agreement with JNJ, JNJ 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, JNJ will generally have control over the further clinical development of JNJ-2113 and any other licensed compounds. JNJ's decisions with respect to such development will affect the timing and availability of potential future payments under the agreement, if any. For example, during the fourth quarter of 2021, a decision was made by JNJ to stop further development of both PTG-200 and PN-232 in favor of JNJ-2113. If the Restated Agreement with JNJ is terminated early, or if JNJ'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 JNJ during the term of the JNJ 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 JNJ regarding the development of JNJ-2113 or other matters under the Restated Agreement with JNJ, such as the interpretation of the agreement or ownership of proprietary rights. Also, because the period of collaborative development under the agreement has ended, JNJ has sole decision-making authority for product candidates resulting from the collaboration, which could lead to disputes with JNJ. Disagreements with JNJ could lead to litigation or arbitration, which would be expensive and would be time-consuming for our management and employees.

Our current and future development and commercialization collaboration may not be successful.

Other than our collaboration with JNJ under the Restated Agreement and our collaboration with Takeda under the Takeda Collaboration Agreement, which is expected to become effective upon the receipt of clearance under the HSR Act, we have no active collaborations for any of our product candidates. Our collaborations with JNJ and Takeda and any future collaboration arrangements may not ultimately be successful, which could have a negative impact on our business, results of operations, financial condition and growth prospects. We do not maintain significant rights or control of future development and commercialization activities under our collaboration with JNJ, or in ex-U.S. territories under our collaboration with Takeda. This could lead to potential disputes in the future over the terms of the collaborations and the respective rights of the parties, and these risks and uncertainties could be present with respect to our potential future collaborations as well.

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

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

We have relied upon and plan to continue to rely upon third-party contract research organizations ("CROs") to execute, monitor and manage clinical trials and collect data for our pre-clinical studies and clinical programs. We control only certain aspects of their activities. We and our CROs are required to comply with GCPs, which are regulations and guidelines promulgated by the FDA, the EMA and comparable foreign regulatory authorities for all of our product candidates in clinical development. If we or any of our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or comparable foreign regulatory authorities may not accept the data or require us to perform additional clinical trials before considering our filing for regulatory approval or approving our marketing application. In addition, significant portions of the clinical studies for our product candidates are expected to be conducted outside of the United States, which will make it more difficult for us to monitor CROs and perform visits of our clinical trial sites and will force us to rely heavily on CROs for 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 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, geopolitical conflict, outbreaks of disease, epidemics and pandemics, such as the COVID-19 pandemic, or otherwise, we could experience delays, disruptions, suspensions or termination of our clinical trial and planned development program, or be required to restart or repeat, any ongoing clinical trials.

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

third-party manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of our product candidates.

Risks Related to Regulatory Approval

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

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

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

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

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

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

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

Risks Related to Commercialization of our Product Candidates

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

We currently do not have a marketing or sales organization for the marketing, sales and distribution of pharmaceutical products, and have only a limited number of employees engaged in those activities. In order to commercialize or co-commercialize any of our product candidates that receive marketing approval, we will have to build adequate marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. We may not be successful in doing so. In the event of the 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. As we have done with Takeda with respect to rusfertide, 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. In the case of the Restated Agreement with JNJ or the Takeda Collaboration Agreement, we may elect to exercise our right to co-detail products, which would require us to establish a U.S. sales team. If we are not successful in commercializing our product candidates, either on our own or through collaborations with one or more third parties, our future revenue will be materially and adversely impacted.

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

In the United States and some foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product candidates for which we obtain marketing approval. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare therapies, which could result in reduced demand for us. See Item 1, “Business – Government Regulation” for additional information.

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

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

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

- the safety and efficacy of the product in clinical trials, and potential advantages over competing treatments;
- the publication of unfavorable safety or efficacy data concerning our product by third parties;
- the prevalence and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the clinical indications for which approval is granted;
- recognition and acceptance of our product candidates over our competitors' products;

- prevalence of the disease or condition for which the product is approved;
- the cost of treatment, particularly in relation to competing treatments;
- the willingness of the target patient population to try our therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- the extent to which the product is approved for inclusion on formularies of hospitals and managed care organizations;
- publicity concerning our products or competing products and treatments;
- the extent to which third-party payors provide coverage and adequate reimbursement for the product candidate, or any other product candidates we may pursue, if approved;
- our ability to maintain compliance with regulatory requirements; and
- labeling or naming imposed by FDA or other regulatory agencies.

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

Risks Related to our Business and Industry

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

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

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

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

Outbreaks of disease, epidemics and pandemics have and could continue to adversely impact our business, including our ongoing and planned clinical trials and pre-clinical and discovery research.

We have experienced delays in our existing and planned clinical trials due to worldwide impacts related to the COVID-19 pandemic, and our future results of operations and liquidity could be adversely impacted by direct and indirect impacts of epidemics and pandemics. We have and could in the future experience additional disruptions or increased expenses that may adversely impact our business, including delays or difficulties in enrolling patients in our ongoing clinical trials and our future clinical trials; delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff or maintaining ongoing operations at such sites; and delays in manufacturing and receiving the supplies, materials and services needed to conduct clinical trials and pre-clinical research.

A continued and prolonged public health crisis could have a material negative impact on our business, financial condition, and operating results.

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

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

There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. A future recession or market correction or other significant geopolitical events could

materially affect our business and the value of our common stock. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals.

We maintain our cash at financial institutions, often in balances that exceed federally-insured limits. The failure of financial institutions could adversely affect our ability to pay our operational expenses or make other payments.

Our cash held in non-interest-bearing and interest-bearing accounts generally exceeds the Federal Deposit Insurance Corporation (the "FDIC") insurance limits. If such banking institutions were to fail, we could lose all or a portion of those amounts held in excess of such insurance limitations. For example, the FDIC took control of Silicon Valley Bank on March 10, 2023. The Federal Reserve subsequently announced that account holders would be made whole. However, the FDIC may not make all account holders whole in the event of future bank failures. In addition, even if account holders are ultimately made whole with respect to a future bank failure, account holders' access to their accounts and assets held in their accounts may be substantially delayed. Any material loss that we may experience in the future or inability for a material time period to access our cash and cash equivalents could have an adverse effect on our ability to pay our operational expenses or make other payments, which could adversely affect our business.

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, we or our collaboration partners are unable to comply with these regulations, our ability to earn potential royalties from sales of product candidates under our collaboration agreements 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 arrangements, or cause our collaboration partners to terminate the related 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. Additionally, the United States has recently experienced historically high levels of inflation and an acute workforce shortage generally, which has created a hyper-competitive wage environment that may increase our operating costs. Any or all of these factors may limit our ability to continue to attract and retain

high quality personnel, which could negatively affect our ability to successfully develop and commercialize product candidates and to grow our business and operations as currently contemplated.

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

As of December 31, 2023, we had 112 full-time equivalent employees, including 85 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 partners, 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, which may expose sensitive data to unauthorized persons. Such data security breaches could lead to the loss of trade secrets or other intellectual property or could lead to the public exposure of personally identifiable information (including sensitive personal information) of our employees, collaborators, clinical trial patients, and others. A malicious intrusion, email compromise or other data security breach or privacy violation that leads to disclosure or modification of or prevents access to patient information, including personally identifiable information or protected health information, could harm our reputation, compel us to comply with federal and/or state breach notification laws, subject us to mandatory corrective action, require us to verify the correctness of database contents and otherwise subject us to liability under laws and regulations that protect personal data, resulting in increased costs or loss of revenue. If we are unable to prevent such data security breaches or privacy violations or implement satisfactory remedial measures, our operations could be disrupted, and we may suffer loss of reputation, financial loss and other regulatory penalties.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials, and produce hazardous waste products. We generally contract with third parties for the disposal of these materials and waste. 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, extreme weather, 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 wildfires. 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. patent covering rusfertide expires in 2034 but is eligible for extension of up to five years for a portion of the time spent in development. Although the life of a patent can be increased based on certain delays caused by the U.S. Patent and Trademark Office, 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 such adverse result or determination could have a material adverse effect on our business, financial condition and results of operations.

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

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

- causing us to lose patent rights in the relevant jurisdiction(s);
- subjecting our collaboration partners or us to litigation, or otherwise preventing the commercialization of product candidates in the relevant jurisdiction(s); or
- requiring our collaboration partners 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 collaborations or cause our collaboration partners to terminate their respective agreements.

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 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, 2023 through December 31, 2023, the reported sale price of our common stock has fluctuated between $10.62 and $30.10 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 on Form 10-K.

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

We are required, pursuant to Section 404 of the Sarbanes-Oxley Act ("Section 404"), to furnish a report by management on the effectiveness of our internal control over financial reporting. This assessment needs to include disclosure of any material weaknesses identified by our management in our internal control over financial reporting. Our public float on June 30, 2023 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 on Form 10-K.

Maintaining adequate internal controls in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that will need to be evaluated frequently. 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. In addition, if we have a material weakness, we will receive an adverse opinion regarding our internal control over financial reporting from our independent registered public accounting firm. 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. If we are not able to comply with the requirements of Section 404 or if we or our independent registered public accounting firm are unable to attest to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our stock could decline and we could be subject to sanctions or investigations by Nasdaq, the SEC, or other regulatory authorities, which would require additional financial and management resources.

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 ("Securities Act"), 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, who are responsible for appointing the members of our management.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibit a person who owns 15% or more of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. Any provision in our Certificate of Incorporation, our Bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock and could also affect the price that some investors are willing to pay for our common stock.

General Risk Factors

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

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

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

Item 1B. Unresolved Staff Comments

None.

Item 1C. Cybersecurity

In the ordinary course of our business, we collect, use, store, and transmit confidential, sensitive, proprietary, and personal information. The secure maintenance of this information and our information technology ("IT") systems is important to our operations and business strategy. To this end, we have documented cybersecurity policies and standards and we assess risks from cybersecurity threats and monitor information systems for potential cybersecurity issues. These processes are managed and monitored by a dedicated cybersecurity team, including third-party service providers and led by our Head of IT, and include mechanisms, controls, technologies, systems, and other processes designed to prevent or mitigate data loss, theft, misuse, or other security incidents or vulnerabilities affecting the data and maintain a stable information technology environment. For example, we use processes and tools to conduct vulnerability testing, data recovery testing, security audits, and ongoing risk assessments, including due diligence on and audits of our key technology vendors, CROs, and other contractors and suppliers. We also conduct regular employee training on matters such as phishing and email security best practices, among other topics. In addition, we consult with outside advisors and experts when appropriate to assist with assessing, identifying, and managing cybersecurity risks, including to anticipate future threats and trends, and their impact on our risk environment.

Our current Head of IT reports directly to our Chief Financial Officer and has over twenty years of experience managing information technology and cybersecurity matters, holds a Master of Science degree in Telecommunications and Computer Networks and is Project Management Professional, Certified Scrum Master and IT Infrastructure Library certified. He, together with our senior leadership team, is responsible for assessing and managing cybersecurity risks. We consider cybersecurity, along with other significant risks that we face, within our overall enterprise risk management framework. In the last fiscal year, we have identified and mitigated certain known cybersecurity threats, which we determined are not reasonably likely to materially affect us, and have strengthened our cybersecurity ecosystem. However, cybersecurity attack techniques change frequently, and with increased volume and sophistication of such attacks there is the potential for us to be adversely affected. Additional information on the cybersecurity risks we face is discussed in Part I, Item 1A, "Risk Factors - Significant disruptions of information technology systems or breaches of data security could adversely affect our business."

Our Board as a whole has oversight for the most significant risks facing us and for our processes to identify, prioritize, assess, manage, and mitigate those risks, including oversight of cybersecurity risks. Our Board receives at least two updates each year on cybersecurity and information technology matters and related risk exposures from our Head of IT as well as other members of our senior leadership team.

Item 2. Properties

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

Item 3. Legal Proceedings

From time to time, we may become subject to litigation and claims arising in the ordinary course of business. We are not currently a party to any material legal proceedings, and we are not currently aware of any pending or threatened legal proceeding against us that we believe could have a material adverse effect on our business, operating results, financial condition or cash flows. Refer to Note 9 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information on our historical legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

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

Stockholders

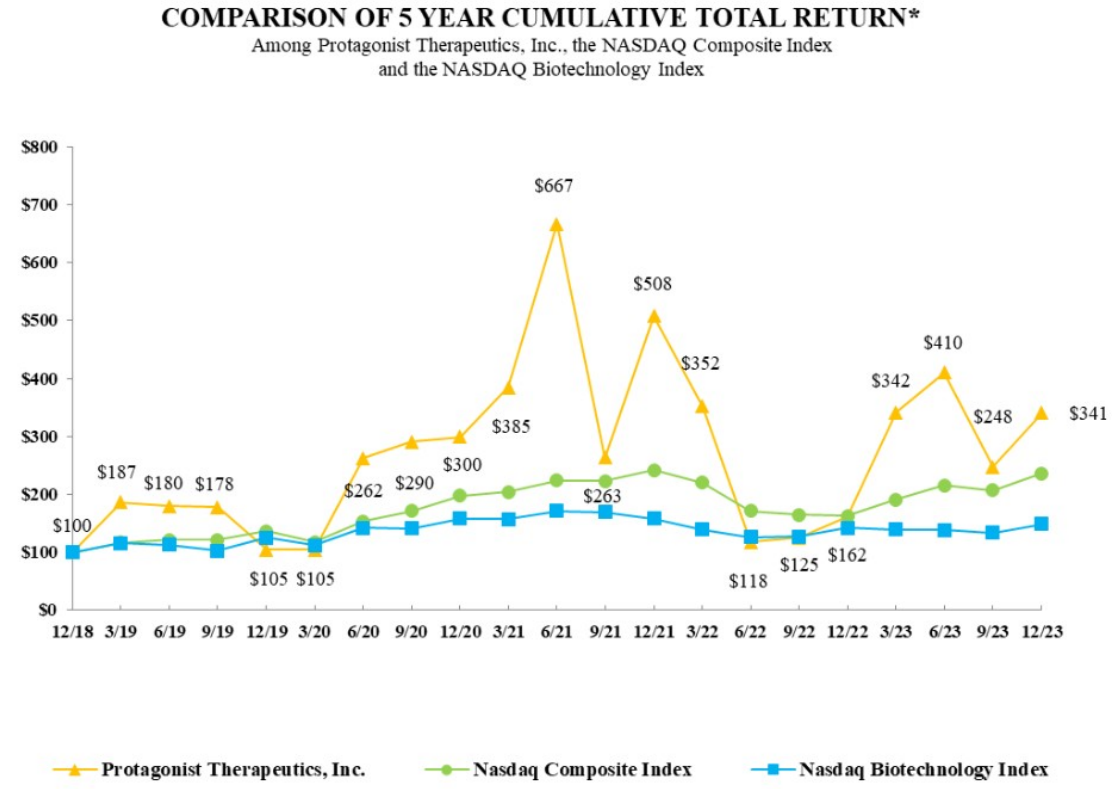
As of the close of business on February 22, 2024, there were two stockholders of record of our common stock. The number of stockholders of record is based upon the actual number of stockholders registered at such date and does not include holders of shares in "street names" or persons, partnerships, associates, or corporations, or other entities identified in security listings maintained by depositories.

Dividends

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

Performance Graph

The following is not deemed "filed" with the Securities and Exchange Commission and shall not be incorporated by reference into any filing we make under the Exchange Act or the Securities Act of 1933, as amended, whether made before or after the date hereof and irrespective of any general incorporation by reference language in such filing. The graph below shows the cumulative total stockholder return assuming an investment on December 31, 2018 in each of our common stock, the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph compares the performance of a $100 investment in our common stock and in each index (assuming reinvestment of all dividends) from December 31, 2018 to December 31, 2023.



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

Recent Sales of Unregistered Securities

None.

Issuer Purchases of Equity Securities

None.

Item 6. Reserved

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

Overview

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

Rusfertide

Our most advanced clinical asset, rusfertide (generic name for PTG-300), is an injectable hepcidin mimetic in development for the potential treatment of polycythemia vera ("PV") and other blood disorders. Hepcidin is a key hormone in regulating iron equilibrium and is critical to the proper development of red blood cells ("RBCs"). Rusfertide mimics the effect of the natural hormone hepcidin, but with greater potency, solubility and stability. Data from our rusfertide Phase 2 clinical trials presented at medical conferences from 2021 through 2023 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. Our rusfertide Phase 2 clinical trials include the following:

- REVIVE, a Phase 2 proof of concept ("POC") trial, was initiated in the fourth quarter of 2019. We completed enrollment of patients in the first quarter of 2022 and 70 patients were enrolled through the end of the randomized withdrawal portion of the trial, which was completed during the first quarter of 2023 and is continuing in an ongoing open-label extension ("OLE");

- THRIVE, a Phase 2 long-term extension trial for REVIVE patients on years three through five of treatment; and

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

In March 2023, we announced positive topline results from the blinded, placebo-controlled, randomized withdrawal portion of the REVIVE trial. Subjects receiving rusfertide achieved statistically significant improvements versus placebo in the trial's primary endpoint. The double-blind, placebo-controlled, 12-week randomized withdrawal portion was included as Part 2 of the REVIVE trial to evaluate rusfertide in PV patients with frequent phlebotomy requirements. In the REVIVE trial, subjects were initially enrolled in the 28-week open label dose-titration and efficacy evaluation Part 1 of the study, followed by 1:1 randomization of 53 subjects to placebo versus rusfertide therapy for a subsequent duration of 12 weeks. More subjects receiving rusfertide during the blinded randomized withdrawal portion of the REVIVE trial were responders compared with placebo (69.2% versus 18.5%, p=0.0003). A trial subject was defined as a responder if the subject completed 12 weeks of double-blind treatment while maintaining hematocrit control without phlebotomy eligibility and without phlebotomy. During the 12 weeks of the blinded randomized withdrawal, 92.3% of subjects on rusfertide (24 out of 26) were not phlebotomized.

Data from the REVIVE trial presented at the European Hematology Association Congress in June 2023 suggested that rusfertide treatment results in highly statistically significant reduction in the need for therapeutic phlebotomy in phlebotomy-dependent patients, leading to rapid, sustained and durable control of hematocrit levels below 45%. Rusfertide was well tolerated, with localized injection site reactions ("ISRs") comprising the majority of adverse events.

Long-term follow up data from the REVIVE trial presented at the American Society of Hematology ("ASH") Annual Meeting in December 2023 showed durable hematocrit control, decreased phlebotomy use, long-term tolerability, and no new safety signals in patients with PV. An analysis of the PACIFIC Phase 2 trial was also presented that indicated rusfertide improves markers of iron deficiency in patients with PV. In addition, data was presented

regarding the prevalence of thromboembolic events and secondary cancers in PV patients not treated with rusfertide. In February 2024, the full Phase 2 REVIVE trial results, including efficacy and safety data, were published in the New England Journal of Medicine.

We have initiated VERIFY, a global double-blind, placebo-controlled Phase 3 clinical trial of rusfertide in PV for approximately 250 patients. We expect enrollment completion by the end of the first quarter of 2024. By the end of 2024, we expect to receive the results of our ongoing two-year study evaluating the carcinogenicity potential of rusfertide when administered once weekly to rats.

In January 2024, we entered into a worldwide license and collaboration agreement for the development and commercialization of rusfertide with Takeda, which is yet to become effective. Under the terms of the agreement, we expect to receive an upfront payment of $300 million and to be eligible to receive additional worldwide development, regulatory and commercial milestone payments of up to $330 million, as well as tiered royalties from 10% to 17% on ex-U.S. net sales. We expect to be responsible for research and development through the completion of the Phase 3 VERIFY trial and U.S. regulatory approval. Takeda is expected to have rights for ex-U.S. development and to be responsible for leading global commercialization activities. We and Takeda expect to also share equally in U.S. profits and losses (50% to us and 50% to Takeda).

Further details related to the agreement, including our right to opt-out of the 50:50 U.S. profit and loss sharing arrangement in exchange for enhanced economics, are available in our Current Report on Form 8-K filed on January 31, 2024 with the U.S. Securities and Exchange Commission (the "SEC"). The effectiveness of the agreement is dependent on and subject to the termination or expiration of any applicable waiting periods under the Hart-Scott-Rodino Act (the "HSR Act").

JNJ-2113 (formerly PN-235)

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

In May 2017, we entered into a worldwide license and collaboration agreement with JNJ, formerly Janssen, to co-develop and co-detail our IL-23R antagonist compounds, including PTG-200 (JNJ-67864238) and certain related compounds for all indications, including inflammatory bowel disease ("IBD"). PTG-200 was a first-generation investigational, orally delivered, IL-23R antagonist for the treatment of IBD. The agreement with JNJ 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 JNJ to independently research and develop collaboration compounds for multiple indications in the IL-23 pathway and further align our financial interests.

Following completion of a Phase 1 trial in the fourth quarter of 2021, a decision was made by JNJ to advance second-generation product candidate JNJ-2113 (JNJ-77242113) based on its superior potency and overall pharmacokinetic and pharmacodynamic profile.

In February 2022, JNJ initiated FRONTIER 1, a 255-patient Phase 2b clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis, which was completed in December 2022. FRONTIER 1 was a randomized, multicenter, double-blind, placebo-controlled trial that evaluated three once-daily dosages and two twice-daily dosages of JNJ-2113 taken orally. The primary endpoint of the trial was the proportion of patients achieving PASI-75 (a 75% improvement in skin lesions as measured by the Psoriasis Area and Severity Index ("PASI")) at 16 weeks. In July 2023, we announced updated positive topline results from the trial, which were presented by JNJ at the World Congress of Dermatology in Singapore. JNJ-2113 achieved the trial's primary and secondary efficacy endpoints. A statistically significant greater proportion of patients who received JNJ-2113 achieved PASI-75 as well as PASI-90 and PASI-100 (90% and 100% improvement, respectively, in skin lesions as measured by the PASI) responses compared to placebo at week 16 in all

five of the trial's treatment groups. A clear dose response was observed across an eight-fold dose range. Treatment was well tolerated, with no meaningful difference in frequency of adverse events across treatment groups versus placebo.

JNJ has initiated five additional JNJ-2113 trials, including:

- ICONIC-LEAD – A 600-patient randomized, controlled Phase 3 trial to evaluate the safety and efficacy of JNJ-2113 compared with placebo in participants with moderate-to-severe plaque psoriasis, with PASI-90 and Investigator's Global Assessment ("IGA") score of 0 (clear) or 1 (almost clear) as co-primary endpoints;

- ICONIC-TOTAL – A 300-patient randomized, controlled Phase 3 trial to evaluate the efficacy and safety of JNJ-2113 compared with placebo for the treatment of plaque psoriasis in participants with at least moderate severity affecting special areas (scalp, genital, and/or palms of the hands and soles of the feet) with overall IGA score of 0 or 1 as the primary endpoint;

- ICONIC ADVANCE 1 – A 750-patient randomized, controlled Phase 3 trial to evaluate the effectiveness of JNJ-2113 in participants with moderate-to-severe plaque psoriasis compared to placebo and Sotyktu ("deucravacitinib"). The trial's primary co-endpoints are PASI-90 and IGA score of 0 or 1;

- ICONIC ADVANCE 2 – A 675-patient Phase 3 trial similarly designed to ICONIC ADVANCE 1, which is expected to start enrolling patients later in 2024; and

- ANTHEM-UC – A 240-patient Phase 2b randomized, controlled trial to evaluate the safety and effectiveness of JNJ-2113 compared with placebo in participants with moderate-to-severely active ulcerative colitis ("UC").

All of the trials in the ICONIC program will use the once-daily, immediate release formulation of JNJ-2113 from the previously completed FRONTIER 1 study. The estimated primary completion date for the ICONIC-LEAD and ICONIC-TOTAL trials is November 2024 (see NCT06095115 and NCT06095102, respectively, at clinicaltrials.gov). The estimated primary completion dates for the ICONIC-ADVANCE 1 and ICONIC-ADVANCE 2 trials are March 2025 and April 2025, respectively (see NCT06143878 and NCT06220604, respectively, at clinicaltrials.gov). The estimated primary completion date for the ANTHEM-UC trial is May 2025 (see NCT06049017 at clinicaltrials.gov). Other Phase 2 trials of JNJ-2113 include the SUMMIT trial for the treatment of moderate-to-severe plaque psoriasis and FRONTIER 2, a long-term extension study, both of which were completed by JNJ in 2023.

We earned a $50.0 million milestone payment upon dosing of the third patient in the ICONIC-TOTAL Phase 3 trial in late October 2023, which we received in December 2023. We earned a $10.0 million milestone payment upon the dosing of the third patient in the ANTHEM Phase 2b trial in UC in December 2023, which we received in January 2024. To date, we have earned $172.5 million in nonrefundable payments from JNJ. We remain eligible for up to approximately $795.0 million in future development and sales milestone payments, inclusive of the potential milestones listed below:

- $115.0 million milestone payment upon JNJ-2113 meeting the co-primary endpoints in any one of the four ICONIC program Phase 3 trials;

- $35.0 million milestone payment upon the filing of a New Drug Application ("NDA") for JNJ-2113 with the U.S. Food and Drug Administration (the "FDA");

- $50.0 million milestone payment upon approval of the NDA by the FDA; and

- $15.0 million milestone payment upon the advancement of JNJ-2113 into a Phase 3 trial in a second indication.

We also remain eligible to receive upward tiering royalties on net product sales at percentages ranging from six percent to ten percent, with ten percent applicable for net sales over $4.0 billion.

At JNJ's Enterprise Business Review in December 2023, JNJ highlighted JNJ-2113 as a potential first- and best-in class targeted oral IL-23 peptide antagonist with potential across multiple indications, including plaque psoriasis, psoriatic arthritis and IBD, with potential peak year sales projection of $5.0 billion plus. JNJ IL-23 monoclonal antibody ("mAb") drugs Stelara and Tremfya generated $14.0 billion in revenues in 2023.

In February 2024, the JNJ-2113 Phase 2b FRONTIER 1 trial results in adults living with moderate-to-severe plaque psoriasis were published in the New England Journal of Medicine.

PN-943

PN-943 is a wholly owned investigational orally delivered gut-restricted alpha 4 beta 7 specific integrin antagonist for IBD. We completed a Phase 2 trial of PN-943 in patients with moderate to severe UC in early 2023. We do not intend to dedicate further internal resources to clinical development or contract manufacturing activities for our PN-943 clinical program.

Discovery Platform

Our clinical assets are all derived from our proprietary discovery platform. Our platform enables us to engineer novel, structurally constrained peptides that are designed to retain key advantages of both orally delivered small molecules and injectable antibody drugs in an effort to overcome many of their limitations as therapeutic agents. Importantly, constrained peptides can be designed to potentially alleviate the fundamental instability inherent in traditional peptides to allow different delivery forms, such as oral, subcutaneous, intravenous, and rectal. Our discovery pipeline has strategically focused on i) hematology and blood disorders and ii) I&I diseases. For example, we have a pre-clinical stage program to identify an orally active hepcidin mimetic, which we believe to be complementary to the injectable rusfertide for offering the best treatment options for PV, hereditary hemochromatosis and other potential erythropoietic and iron imbalance disorders.

In January 2024, we announced a new oral Interleukin-17 ("IL-17") peptide antagonist program targeting three IL-17 dimers (IL-17 AA, AF and FF) which may offer potential treatment options for hidradenitis suppurativa ("HS"), spondyloarthritis ("SpA"), plaque psoriasis and psoriatic arthritis. Our preliminary results showed similar or better in vitro potency than the currently approved drugs Cosentyx® and Taltz®. We expect to nominate a development candidate by the end of 2024.

Business Update

We are currently operating in a period of economic uncertainty and capital markets disruption, which has been impacted by domestic and global monetary and fiscal policy, geopolitical instability, ongoing military conflicts, including between Russia and Ukraine and in Israel and surrounding areas, rising tensions between China and Taiwan, a recessionary environment, historically high domestic and global inflation, high interest rates and instability in banks and other financial institutions. Our future results of operations and liquidity could be adversely impacted by outbreaks of disease, epidemics and pandemics, including potential further delays in existing and planned clinical trials, difficulty in recruiting patients for these clinical trials, delays in manufacturing and collaboration activities and supply chain disruptions. The conflict in Ukraine has exacerbated market disruptions, including significant volatility in commodity prices, as well as supply chain interruptions, and has contributed to record inflation globally. The U.S. Federal Reserve and other central banks may be unable to contain inflation through more restrictive monetary policy and inflation may increase or continue for a prolonged period of time. Inflationary factors, such as increases in the cost of clinical supplies, interest rates, overhead costs and transportation costs may adversely affect our operating results. Also, the failure of Silicon Valley Bank and other regional banks in the United States during the first half of 2023 has given rise to uncertainty in the security of amounts in deposit accounts uninsured by the Federal Deposit Insurance Corporation. We continue to monitor these events and the potential impact on our business. Although we do not believe that inflation has had a material adverse impact on our financial position or results of operations to date, our financial position or results of

operations may be adversely affected in the future due to numerous factors, including domestic and global monetary and fiscal policy, supply chain constraints, consequences associated with ongoing military conflicts, including between Russia and Ukraine and in Israel and surrounding areas, and other factors, and such factors may lead to increases in the cost of manufacturing our product candidates and delays in initiating trials.

Operations

We have incurred net losses in each year since inception and we do not anticipate achieving sustained profitability in the foreseeable future. Our net losses were $79.0 million, $127.4 million and $125.6 million for the years ended December 31, 2023, 2022 and 2021, respectively. As of December 31, 2023, we had an accumulated deficit of $615.7 million. Substantially all of our net losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to continue to incur significant research and development expenses and other expenses related to our ongoing operations, product development, and pre-commercialization activities. As a result, we expect to continue to incur losses in the future as we continue our development of, and seek regulatory approval for, our product candidates.

JNJ License and Collaboration Agreement

On July 27, 2021, we entered into an Amended and Restated License and Collaboration Agreement (the "Restated Agreement") with JNJ, which amended and restated the License and Collaboration Agreement, effective July 13, 2017, by and between us and JNJ (the "Original Agreement"), as amended by the first amendment, effective May 7, 2019 (the "First Amendment"). Prior to January 1, 2023, JNJ was a related party to us as Johnson & Johnson Innovation - JJDC, Inc. was a significant (greater than 5%) stockholder of the Company, and both companies are subsidiaries of Johnson & Johnson. Upon the effectiveness of the Original Agreement, we received a non-refundable, upfront cash payment of $50.0 million from JNJ. Upon the effectiveness of the First Amendment, we received a $25.0 million payment from JNJ in 2019. In the first quarter of 2020, we received a $5.0 million payment triggered by the successful nomination of a second-generation IL-23R antagonist development compound. In the fourth quarter of 2021, we received a $7.5 million milestone payment from JNJ triggered by completion of the data collection for JNJ-2113 Phase 1 activities. In the second quarter of 2022, we received a $25.0 million milestone payment in connection with the dosing of a third patient in FRONTIER 1 during the first quarter of 2022. In the fourth quarter of 2023, we received a $50.0 million milestone payment from JNJ in connection with the dosing of the third patient in the ICONIC-LEAD Phase 3 clinical trial of JNJ-2113 in patients with moderate-to-severe psoriasis. In the first quarter of 2024, we received a $10.0 million milestone payment from JNJ in connection with the dosing of the third patient in connection with the ANTHEM Phase 2b clinical trial of JNJ-2113 in patients with UC in the fourth quarter of 2023. We have earned a total of $172.5 million in non-refundable payments from JNJ since the inception of the Restated Agreement in 2017 through the date of this report. See Note 3 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Takeda Collaboration Agreement

In January 2024, we entered into a worldwide license and collaboration agreement for the development and commercialization of rusfertide with Takeda (the "Takeda Collaboration Agreement"), which is yet to become effective. See Note 15 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 U.S. generally accepted accounting principles ("GAAP"). The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent liabilities at the date of the consolidated financial statements, as well as the reported revenue generated, and the expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, and the results of which form the basis for making judgments about the carrying

value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Use of Estimates

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

There has been uncertainty and disruption in the global economy and financial markets due to a number of factors, including geopolitical instability, inflationary pressures, high interest rates, instability in banks and other financial institutions and domestic and global monetary and fiscal policy. We have taken into consideration any known impacts of these factors in our accounting estimates to date and are not aware of any additional specific events or circumstances that would require any additional updates to our estimates or judgments or a revision of the carrying value of our assets or liabilities as of the date of the filing of this Annual Report on Form 10-K. These estimates may change as new events occur, circumstances change, 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 for each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

Milestone payments: At the inception of each arrangement or amendment that includes development, regulatory or commercial milestone payments, we evaluate whether the milestones are considered probable of being reached and

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

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

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

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

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

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

Research and Development Costs

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

We accrue for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of pre-clinical studies and clinical trials, and contract manufacturing activities. We record the estimated costs of research and development activities based upon the estimated services provided but not yet invoiced and we include these costs in accrued expenses and other payables in our consolidated balance sheets and within research and development expense in our consolidated statements of operations. We accrue for these costs based on various factors such as estimates of the work completed and in accordance with agreements established with our third-party service providers. As actual costs become known, we adjust our accrued liabilities. We have not experienced any material differences between accrued liabilities and actual costs incurred. However, the status and timing of actual services performed, number of patients enrolled, the rate of patient enrollment and the number and location of sites activated may vary from our estimates and may result in adjustments to our research and development expenses in future periods. Changes in these estimates that result in material changes to our accruals could materially affect the results of our 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 JNJ 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. For the year ended December 31, 2024, we expect to recognize license and collaboration revenue from payments we are eligible to receive under the Takeda Collaboration Agreement, which is yet to become effective. The effectiveness of the agreement and our receipt of payments thereunder is dependent on and subject to the termination or expiration of any applicable waiting periods under the HSR Act. See Note 15 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 trial 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 and non-clinical studies and clinical trials;
- 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 administrative supplies.

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

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

We expect our research and development expenses to increase in the near term as compared to prior year periods as we continue to focus our resources toward progressing our rusfertide program into later stage clinical trials and preparing for commercialization. We do not intend to dedicate further internal resources to clinical development or contract manufacturing activities for our PN-943 clinical program. The process of conducting research, identifying potential product candidates and conducting pre-clinical studies 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 be able to 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 administrative supplies. We expect to continue to incur expenses to support our continued operations as a public company, including expenses related to compliance with the rules and regulations of the SEC and those of the national securities exchange on which our securities are traded, insurance expenses, investor relations expenses, audit fees, professional services and general overhead and administrative costs.

Interest Income

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

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 Years Ended December 31, 2023 and 2022

	Year Ended December 31,		Dollar Change	% Change
	2023	2022		
	(Dollars in thousands)			
License and collaboration revenue	$ 60,000	$ 26,581	$ 33,419	126
Operating expenses:				
Research and development [1]	120,161	126,215	(6,054)	(5)
General and administrative [2]	33,491	31,739	1,752	6
Total operating expenses	153,652	157,954	(4,302)	(3)
Loss from operations	(93,652)	(131,373)	37,721	(29)
Interest income	14,898	4,060	10,838	267
Other expense, net	(201)	(80)	(121)	151
Net loss	$ (78,955)	$ (127,393)	$ 48,438	(38)

[1] Includes $17.1 million and $14.7 million of non-cash stock-based compensation expense for the years ended December 31, 2023 and 2022, respectively.

[2] Includes $12.2 million and $9.5 million of non-cash stock-based compensation expense for the years ended December 31, 2023 and 2022, respectively.

License and Collaboration Revenue

License and collaboration revenue increased $33.4 million, or 126%, from $26.6 million for the year ended December 31, 2022 to $60.0 million for the year ended December 31, 2023. The increase in revenue was primarily due to milestone payments earned under our license and collaboration agreement with JNJ during the fourth quarter of 2023, including a $50.0 million milestone payment upon dosing of the third patient in the ICONIC-LEAD Phase 3 trial of JNJ-2113 in patients with moderate-to-severe psoriasis, and a $10.0 million milestone payment upon the dosing of the third patient in the ANTHEM-UC Phase 2b trial in UC. License and collaboration revenue for the year ended December 31, 2022 was primarily related to the transaction price under the license and collaboration agreement with JNJ recognized based on proportional performance. We completed our performance obligation under the license and collaboration agreement with JNJ as of June 30, 2022.

Research and Development Expenses

	Year Ended December 31,		Dollar	%
	2023	2022	Change	Change
	(Dollars in thousands)			
Clinical and development expense — rusfertide (PTG-300)	$ 98,060	$ 64,789	$ 33,271	51
Clinical and development expense — PN-943	1,058	36,906	(35,848)	(97)
Clinical and development expense — JNJ-2113 (PN-235)	99	201	(102)	(51)
Clinical and development expense — Other	—	657	(657)	(100)
Preclinical and drug discovery research expense	20,944	23,704	(2,760)	(12)
Grants and tax incentives expense reimbursement, net	—	(42)	42	(100)
Total research and development expenses	$ 120,161	$ 126,215	$ (6,054)	(5)

Research and development expenses decreased $6.0 million, or 5%, from $126.2 million for the year ended December 31, 2022 to $120.2 million for the year ended December 31, 2023. The decrease was primarily due to (i) a decrease of $35.8 million in expenses for the PN-943 program, and (ii) a decrease of $2.8 million in expenses related to pre-clinical and drug discovery research expense, partially offset by (iii) an increase of $33.3 million in rusfertide clinical and contract manufacturing expenses primarily for the Phase 3 VERIFY clinical trial. We completed a Phase 2 trial of PN-943 in patients with moderate to severe UC in early 2023, following which we de-prioritized further development work.

We had 85 and 82 full-time equivalent research and development employees as of December 31, 2023 and 2022, respectively. Research and development personnel-related expenses for the year ended December 31, 2023 increased by $1.1 million as compared to the year ended December 31, 2022 primarily due to an increase of $2.3 million in stock-based compensation expense, partially offset by a decrease of $1.2 million of other personnel-related expenses.

General and Administrative Expenses

General and administrative expenses increased $1.8 million, or 6%, from $31.7 million for the year ended December 31, 2022 to $33.5 million for the year ended December 31, 2023 primarily due to an increase in stock-based compensation expense during the current year period, partially offset by one-time costs incurred during the first quarter of 2022.

We had 27 and 23 full-time equivalent general and administrative employees as of December 31, 2023 and 2022, respectively.

Interest Income

Interest income increased $10.8 million, or 267%, from $4.1 million for the year ended December 31, 2022 to $14.9 million for the year ended December 31, 2023. This increase was primarily due to higher invested balances and higher yields due to increased interest rates compared to the prior year period.

Comparison of the Years Ended December 31, 2022 and 2021

See Part II, Item 7—Results of Operations—Comparison of the Years Ended December 31, 2022 and 2021 in our Annual Report on Form 10-K for the year ended December 31, 2022, filed on March 15, 2023, for a discussion of our results of operations for the year ended December 31, 2022 compared to the year ended December 31, 2021.

Liquidity and Capital Resources

Sources of Liquidity

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

Proceeds from Sales of Our Common Stock

In April 2023, we completed an underwritten public offering of 5,000,000 shares of our common stock at a public offering price of $20.00 per share and issued an additional 750,000 shares of common stock at a price of $20.00 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 approximately $107.8 million.

In August 2022, we entered into an Open Market Sale Agreement℠, pursuant to which we may offer and sell up to $100.0 million shares of our common stock from time to time in "at-the-market" offerings (the "2022 ATM Facility"). During the three months ended March 31, 2023, we sold 1,749,199 shares of our common stock under the 2022 ATM Facility for net proceeds of $24.3 million, after deducting issuance costs. There were no sales of our common stock under the 2022 ATM Facility during the three months ended June 30, 2023, September 30, 2023 or December 31, 2023. There were no sales of our common stock under the 2022 ATM Facility during the year ended December 31, 2022.

In August 2018, we entered into a Securities Purchase Agreement with certain accredited investors (each, an "Investor" and, collectively, the "Investors"), pursuant to which we sold an aggregate of 2,750,000 shares of our common stock at a price of $8.00 per share for aggregate net proceeds of $21.7 million, after deducting offering expenses payable by us. In a concurrent private placement, we issued the Investors warrants to purchase an aggregate of 2,750,000 shares of our common stock (each, a "Warrant" and, collectively, the "Warrants"). Each Warrant was exercisable from August 8, 2018 through August 8, 2023. Warrants to purchase 1,375,000 shares of our common stock had an exercise price of $10.00 per share and Warrants to purchase 1,375,000 shares of our common stock had an exercise price of $15.00 per share. The exercise price and number of shares of our common stock issuable upon the exercise of the Warrants (the "Warrant Shares") were 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 were exercisable on a "cashless" basis. In connection with the issuance and sale of the common stock and Warrants, we granted the Investors certain registration rights with respect to the Warrants and the Warrant Shares. The common stock and Warrants met the criteria for equity classification, and the net proceeds from the transaction were recorded as a credit to additional paid-in capital.

In August 2023, prior to the expiration of the Warrants, we entered into certain agreements with the Investors and their affiliates under which we agreed to allow the Warrants to be exercised in exchange for pre-funded warrants representing the same number of Warrant Shares underlying the Warrants with an exercise price of $0.001 per share (the "Pre-Funded Warrants"). Subsequent to the execution of the agreements and prior to the expiration of the Warrants, all outstanding Warrants were exercised for gross proceeds of $34.4 million in exchange for 44,748 shares of our common stock and Pre-Funded Warrants to purchase 2,705,252 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 Pre-Funded Warrants) with an exercise price of $0.001 per share. The Pre-Funded Warrants will expire upon the day they are exercised in full. The Pre-Funded Warrants are exercisable at any time prior to expiration except that the Pre-Funded Warrants cannot be exercised by the Investors if, after giving effect thereto, the Investors would beneficially own more than 9.99% of our common stock, subject to certain exceptions. The common stock and Pre-Funded Warrants met the criteria for equity classification and the net proceeds from the transaction were recorded as a credit to additional paid-in capital. In accordance with Accounting Standards Codification Topic 260, *Earnings Per Share*, outstanding Pre-Funded 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. As of December 31, 2023, none of the Pre-Funded Warrants have been exercised.

Receipt of Payments Under Collaboration Agreements

We have earned $172.5 million in non-refundable payments from JNJ since the inception of the Restated Agreement in 2017 through the date of this Annual Report on Form 10-K as follows:

- Upon effectiveness of the Original Agreement, we received a non-refundable, upfront cash payment of $50.0 million from JNJ in 2017;
- Upon effectiveness of the First Amendment, we became eligible to receive a $25.0 million payment from JNJ, which was received during the second quarter of 2019;
- In December 2019, we became eligible to receive a $5.0 million payment triggered by the successful nomination of a second-generation development compound, which was received during the first quarter of 2020;
- In October 2021, we became eligible to receive a $7.5 million milestone payment triggered by completion of the data collection for JNJ-2113 (formerly PN-235) Phase 1 activities, which was received during the fourth quarter of 2021;
- In March 2022, we became eligible to receive a $25.0 million milestone payment in connection with the dosing of the third patient in the Phase 2b clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis, which was received during the second quarter of 2022;
- In October 2023, we became eligible to receive a $50.0 million milestone payment in connection with the dosing of the third patient in the ICONIC-TOTAL Phase 3 clinical trial of JNJ-2113 in moderate-to-severe plaque psoriasis, which was received in December 2023; and
- In December 2023, we became eligible to receive a $10.0 million milestone payment in connection with the dosing of the third patient in the ANTHEM Phase 2b clinical trial of JNJ-2113 in ulcerative colitis, which was received in January 2024.

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

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

- $115.0 million upon a Phase 3 clinical trial for a second-generation compound for any indication meeting its primary clinical endpoint;
- $35.0 million upon the filing of an NDA for a second-generation compound with the FDA;
- $50.0 million upon FDA approval of an NDA for a second-generation compound; and
- $15.0 million upon the dosing of the third patient in a Phase 3 clinical trial for a second-generation compound for a second indication.

Capital Requirements

As of December 31, 2023, we had $341.6 million of cash, cash equivalents and marketable securities and an accumulated deficit of $615.7 million. Our capital expenditures were $0.6 million, $0.8 million and $1.1 million for the years ended December 31, 2023, 2022 and 2021, respectively. Our primary uses of cash are to fund our operating

expenses, primarily related to our research and development expenditures and general and administrative costs. We expect that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operations for at least the next twelve months from the date of this Annual Report on Form 10-K based on current operating plans and financial forecasts.

In January 2024, we entered into a worldwide license and collaboration agreement for the development and commercialization of rusfertide with Takeda, which is yet to become effective. See Note 15 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

We may require additional funding to advance our early discovery pipeline and to develop, acquire, or in-license other potential product candidates. Our future funding requirements will depend on many factors, including:

- the progress, timing, scope, results and costs of advancing our clinical trials for our product candidates, including the ability to enroll patients in a timely manner for our clinical trials;
- the costs of and our ability to obtain clinical and commercial supplies for our current product candidates and any other product candidates we may identify and develop;
- our ability to successfully commercialize our current product candidates and any other product candidates we may identify and develop;
- the success of our existing or future collaborations with third parties;
- the selling and marketing costs associated with our current product candidates and any other product candidates we may identify and develop, including the costs and timing of expanding our sales and marketing capabilities;
- the achievement of development, regulatory and sales milestones resulting in payments to us from JNJ under the Restated Agreement, Takeda under the Takeda Collaboration Agreement or other such arrangements that we may enter into, and the timing of receipt of such payments, if any;
- the timing, receipt and amount of royalties from JNJ under the Restated Agreement or Takeda under the Takeda Collaboration Agreement upon regulatory approval or clearance, if any;
- the amount and timing of sales and other revenues from our current product candidates and any other product candidates we may identify and develop, including the sales price and the availability of adequate third-party reimbursement;
- the cash requirements of any future acquisitions or discoveries of product candidates;
- the time and costs necessary to respond to technological and market developments;
- the extent to which we may acquire or in-license other product candidates and technologies;

Such additional funding may come from various sources, including raising additional capital, seeking access to debt, and seeking additional collaborative or other arrangements with partners, but such funding may not be available on terms acceptable to us, if at all. As discussed in Part I, Item 1A,"Risk Factors," we are currently operating in a period of macroeconomic uncertainty and capital markets disruption, which has been significantly impacted by domestic and global monetary and fiscal policy, geopolitical instability, inflationary pressures, high interest rates and banking and other financial institution instability, among other factors. A future recession or market correction, including those due to significant geopolitical or macroeconomic events, could materially affect our business and our access to credit and financial markets.

Any failure to raise capital as and when needed could have a negative impact on our financial condition and on our ability to pursue our business plans and strategies. Further, our operating plans may change, and we may need additional funds to meet operational needs and capital requirements for clinical trials, other research and development activities and pre-commercialization costs. If we do raise additional capital through public or private equity offerings or convertible debt securities, the ownership interest of our existing stockholders could be diluted, and the terms of these securities could include liquidation or other preferences that could adversely affect our stockholders' rights. If we raise additional capital through debt financing, we could be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. Because of the numerous risks and uncertainties associated with the development and commercialization of our product candidates, we are unable to fully estimate the amounts of increased capital outlays and operating expenditures associated with our current and anticipated product development programs. For additional information, see Part I, Item 1A, "Risk Factors — Risks Related to our Financial Position and Capital Requirements."

The following table summarizes our cash flows for the periods indicated:

	Year Ended December 31,		
	2023	2022	2021
Consolidated Statements of Cash Flows Data:	(Dollars in thousands)		
Cash used in operating activities	$ (70,236)	$ (108,137)	$ (107,865)
Cash (used in) provided by investing activities	$ (39,258)	$ 91,468	$ (15,860)
Cash provided by financing activities	$ 170,477	$ 18,838	$ 129,923
Stock-based compensation	$ 29,293	$ 24,202	$ 16,395

Cash Used in Operating Activities

Cash used in operating activities for the year ended December 31, 2023 was $70.2 million, consisting primarily of our net loss of $79.0 million and a net change of $19.5 million in net operating assets and liabilities, partially offset by certain non-cash items, including $29.2 million of stock-based compensation expense. The $37.9 million decrease in cash used in operating activities for the year ended December 31, 2023, as compared to the year ended December 31, 2022, was primarily due to a $48.4 million decrease in our net loss and a $5.1 million increase in stock-based compensation expense, partially offset by a $4.0 million decrease in accretion of discount on marketable securities and an $11.7 million net change in net operating assets and liabilities.

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

Cash (Used in) Provided by Investing Activities

Cash used in investing activities for the year ended December 31, 2023 was $39.3 million, consisting of purchases of marketable securities of $191.1 million and purchases of property and equipment of $0.6 million, partially offset by proceeds from maturities of marketable securities of $152.4 million. The $130.7 million decrease in cash provided by investing activities for the year ended December 31, 2023, as compared to the year ended December 31, 2022, was primarily related to a decrease in the net activity of purchases and maturities of marketable securities. Purchases of property and equipment were primarily related to purchases of laboratory and computer equipment.

Cash provided by investing activities for the year ended December 31, 2022 was $91.5 million, consisting of proceeds from maturities of marketable securities of $307.1 million, partially offset by purchases of marketable securities of $214.9 million and purchases of property and equipment of $0.8 million. The $107.3 million increase in cash provided by investing activities for the year ended December 31, 2022, as compared to the year ended December

31, 2021, was primarily related to a decrease of $71.7 million in purchases of marketable securities and an increase of $35.3 million in proceeds from maturities of marketable securities. Purchases of property and equipment were primarily related to purchases of laboratory and computer equipment.

Cash Provided by Financing Activities

Cash provided by financing activities for the year ended December 31, 2023 was $170.5 million, consisting primarily of net cash proceeds of $107.8 million from the April 2023 public offering of our common stock, $24.3 million from sales of our common stock under the 2022 ATM Facility, $34.4 million from the exercise of the Warrants in exchange for issuance of Pre-Funded Warrants and common stock, and $4.8 million in proceeds from the issuance of common stock upon exercise of stock options and purchases of common stock under our employee stock purchase plan. The $151.6 million increase in cash provided by financing activities for the year ended December 31, 2023, as compared to the year ended December 31, 2022, was primarily due to a $107.8 million increase in net cash proceeds from the April 2023 public offering, a $9.7 million increase in cash proceeds from ATM sales and a $34.4 million increase in net cash proceeds from the exercise of the Warrants.

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

Contractual Obligations and Other Commitments

In the normal course of business, we enter into agreements with contract service providers to assist in the performance of our research and development activities and clinical and commercial manufacturing activities. Subject to the required notice periods and our obligations under certain 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. In July 2021, we entered into a second amendment to our facility lease agreement dated as of March 2017 to lease approximately 15,000 square feet of additional office space in Newark, California. See Note 8 to the Consolidated Financial Statements elsewhere in this Annual Report on Form 10-K for additional information.

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

In January 2024, we entered into the Takeda Collaboration Agreement, which is yet to become effective. See Note 15 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

In June 2012, we entered into the Zealand Agreement to identify, optimize and develop novel disulfide-rich peptides to discover a hepcidin mimetic. We amended the Zealand Agreement in February 2014, at which point we assumed responsibility for the development program. In January 2020, we initiated arbitration proceedings with the International Court of Arbitration of the International Chamber of Commerce against Zealand. In August 2021, we and

Zealand agreed to resolve the dispute and reached an Arbitration Resolution Agreement. See Note 7 and Note 9 to the Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for additional information.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

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

Interest Rate Fluctuation Risk

We had $341.6 million and $237.4 million in cash, cash equivalents and marketable securities at December 31, 2023 and 2022, respectively. Our cash and cash equivalents consist of cash, money market funds, commercial paper and government bonds. Marketable securities consist of certificates of deposit, corporate bonds, commercial paper and government bonds. A portion of our investments are interest-bearing instruments carrying a degree of interest rate risk. However, because our investments are of high-quality credit rating and are short term in duration, we believe that our exposure to interest rate risk is not significant and that a hypothetical 100 basis point change in interest rates would not have a significant impact on the total value of our portfolio.

Approximately $0.9 million and $2.5 million of our cash balance was located in Australia at December 31, 2023 and 2022, respectively. Our expenses, except those related to our Australian operations, are generally denominated in U.S. dollars. For our operations in Australia, the majority of our expenses are denominated in Australian dollars. To date, we have not had a formal hedging program with respect to foreign currency, but we may do so in the future if our exposure to foreign currency becomes more significant. A 10% increase or decrease in current exchange rates would not have a material effect on the results of our operations.

Inflation Fluctuation Risk

The inflationary environment has decreased over the period covered by this Annual Report on Form 10-K as compared to prior year periods. Inflation generally affects us by increasing our costs, such as the cost of labor and research and development contract costs. We do not believe inflation has had a material effect on the results of our operations during the year ended December 31, 2023.

Item 8. Financial Statements and Supplementary Data

PROTAGONIST THERAPEUTICS, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Protagonist Therapeutics, Inc. (the Company) as of December 31, 2023 and 2022, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2023, 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, 2023 and 2022, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2023, 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, 2023, 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 27, 2024 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 Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the account or disclosure to which it relates.

Accrued clinical and research related expenses

Description of the Matter

At December 31, 2023, the Company has accrued $11.8 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 and research related expenses 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 and research related expenses, 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 accruals recorded for services incurred by third parties by understanding the terms and timeline of significant projects and evaluating management's determination of work performed at the balance sheet date. Further, we inspected selected invoices received from third parties after the balance sheet date and evaluated whether services performed prior to the balance sheet date had been properly included in costs accrued.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2020.
San Mateo, California
February 27, 2024

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

	December 31, 2023	December 31, 2022
Assets		
Current assets:		
Cash and cash equivalents	$ 186,727	$ 125,744
Marketable securities	154,890	111,611
Receivable from collaboration partner	10,000	10
Prepaid expenses and other current assets	3,960	5,712
Total current assets	355,577	243,077
Property and equipment, net	1,195	1,565
Restricted cash - noncurrent	225	225
Operating lease right-of-use asset	954	3,061
Total assets	$ 357,951	$ 247,928
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 772	$ 3,640
Payable to collaboration partner	3	69
Accrued expenses and other payables	19,358	24,955
Operating lease liability - current	1,141	2,515
Total current liabilities	21,274	31,179
Operating lease liability - noncurrent	—	1,141
Total liabilities	21,274	32,320
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; 57,708,613 and 49,339,252 shares issued and outstanding as of December 31, 2023 and 2022, respectively	1	—
Additional paid-in capital	952,491	752,722
Accumulated other comprehensive loss	(105)	(359)
Accumulated deficit	(615,710)	(536,755)
Total stockholders' equity	336,677	215,608
Total liabilities and stockholders' equity	$ 357,951	$ 247,928

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,		
	2023	2022	2021
License and collaboration revenue	$ 60,000	$ 26,581	$ 27,357
Operating expenses:			
Research and development	120,161	126,215	126,006
General and administrative	33,491	31,739	27,196
Total operating expenses	153,652	157,954	153,202
Loss from operations	(93,652)	(131,373)	(125,845)
Interest income	14,898	4,060	443
Other expense, net	(201)	(80)	(149)
Net loss	$ (78,955)	$ (127,393)	$ (125,551)
Net loss per share, basic and diluted	$ (1.39)	$ (2.60)	$ (2.71)
Weighted-average shares used to compute net loss per share, basic and diluted	56,763,559	49,042,232	46,322,910

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,		
	2023	2022	2021
Net loss	$ (78,955)	$ (127,393)	$ (125,551)
Other comprehensive loss:			
Gain (loss) on translation of foreign operations	194	(149)	(182)
Unrealized gain (loss) on marketable securities	60	89	(145)
Comprehensive loss	$ (78,701)	$ (127,453)	$ (125,878)

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

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

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Gain	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 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 income (loss)	—	—	—	(327)	—	(327)
Net loss	—	—	—	—	(125,551)	(125,551)
Balance at December 31, 2021	47,838,330	—	709,682	(299)	(409,362)	300,021
Issuance of common stock pursuant to at-the-market offering, net of issuance costs	422,367	—	14,553	—	—	14,553
Issuance of common stock under equity incentive and employee stock purchase plans	686,284	—	4,448	—	—	4,448
Issuance of common stock upon exercise of Exchange Warrants	399,997	—	—	—	—	—
Shares withheld for net settlement of tax withholding upon vesting of restricted stock units	(7,726)	—	(188)	—	—	(188)
Stock-based compensation expense	—	—	24,202	—	—	24,202
Issuance costs related to prior period common stock offering	—	—	25	—	—	25
Other comprehensive income (loss)	—	—	—	(60)	—	(60)
Net loss	—	—	—	—	(127,393)	(127,393)
Balance at December 31, 2022	49,339,252	—	752,722	(359)	(536,755)	215,608
Issuance of common stock pursuant to public offerings, net of issuance costs	5,750,000	—	107,798	—	—	107,798
Issuance of common stock pursuant to at-the-market offering, net of issuance costs	1,749,199	1	24,301	—	—	24,302
Exercise of Warrants in exchange for issuance of Pre-Funded Warrants	—	—	33,813	—	—	33,813
Issuance of common stock upon exercise of Warrants	44,748	—	559	—	—	559
Issuance of common stock under equity incentive and employee stock purchase plans	857,377	—	4,774	—	—	4,774
Shares withheld for net settlement of tax withholding upon vesting of restricted stock units	(31,963)	—	(769)	—	—	(769)
Stock-based compensation expense	—	—	29,293	—	—	29,293
Other comprehensive income (loss)	—	—	—	254	—	254
Net loss	—	—	—	—	(78,955)	(78,955)
Balance at December 31, 2023	57,708,613	$ 1	$ 952,491	$ (105)	$ (615,710)	$ 336,677

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,		
	2023	2022	2021
Cash Flows from Operating Activities			
Net loss	$ (78,955)	$ (127,393)	$ (125,551)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation	29,293	24,202	16,395
Operating lease right-of-use asset amortization	2,335	2,335	1,962
(Accretion) amortization of discount/premium on marketable securities	(4,569)	(549)	1,830
Depreciation	977	1,034	813
Other	194	—	—
Changes in operating assets and liabilities:			
Research and development tax incentive receivable	—	2,686	(1,775)
Receivable from collaboration partner	(9,990)	1,556	860
Prepaid expenses and other assets	1,753	3,754	(3,227)
Accounts payable	(2,868)	2,045	(1,390)
Payable to collaboration partner	(66)	(830)	(1,833)
Accrued expenses and other payables	(5,597)	(12,715)	19,097
Deferred revenue	—	(1,601)	(12,876)
Operating lease liability	(2,743)	(2,661)	(2,049)
Other liabilities	—	—	(121)
Net cash used in operating activities	(70,236)	(108,137)	(107,865)
Cash Flows from Investing Activities			
Purchase of marketable securities	(191,045)	(214,874)	(286,589)
Proceeds from maturities of marketable securities	152,396	307,137	271,830
Purchases of property and equipment	(609)	(795)	(1,101)
Net cash (used in) provided by investing activities	(39,258)	91,468	(15,860)
Cash Flows from Financing Activities			
Proceeds from public offering of common stock, net of issuance costs	107,798	—	123,829
Proceeds from at-the-market offering, net of issuance costs	24,302	14,553	—
Proceeds from exercise of Warrants in exchange for issuance of Pre-Funded Warrants	33,813	—	—
Proceeds from issuance of common stock upon exercise of Warrants	559	—	—
Proceeds from issuance of common stock upon exercise of stock options and purchases under employee stock purchase plan	4,774	4,448	6,283
Tax withholding payments related to net settlement of restricted stock units	(769)	(188)	(189)
Issuance costs related to prior period common stock offering	—	25	—
Net cash provided by financing activities	170,477	18,838	129,923
Effect of exchange rate changes on cash, cash equivalents and restricted cash	—	(90)	(126)
Net increase in cash, cash equivalents and restricted cash	60,983	2,079	6,072
Cash, cash equivalents and restricted cash, beginning of period	125,969	123,890	117,818
Cash, cash equivalents and restricted cash, end of period	$ 186,952	$ 125,969	$ 123,890
Supplemental Disclosure of Non-Cash Financing and Investing Information:			
Purchases of property and equipment in accounts payable and accrued liabilities	$ 61	$ 19	$ 143
Issuance costs related to common stock offering included in accrued liabilities and other payables	$ —	$ —	$ 25

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 peptide-based new chemical entities rusfertide and JNJ-2113 (formerly PN-235) in advanced stages of clinical development, both derived from the Company's proprietary technology platform. The Company's clinical programs fall into two broad categories of diseases: (i) hematology and blood disorders, and (ii) inflammatory and immunomodulatory diseases. The Company has one wholly owned subsidiary, Protagonist Pty Limited ("Protagonist Australia"), located in Brisbane, Queensland, Australia.

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

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

Liquidity

As of December 31, 2023, the Company had cash, cash equivalents and marketable securities of $341.6 million. The Company has incurred net losses from operations since inception and had an accumulated deficit of $615.7 million as of December 31, 2023. The Company's ultimate success depends upon the outcome of its research and development and collaboration activities. The Company expects to incur additional losses in the future and anticipates the need to raise additional capital to continue to execute its long-range business plan. Since the Company's initial public offering in August 2016, it has financed its operations primarily through proceeds from offerings of common stock and payments received under license and collaboration agreements.

Risks and Uncertainties

The Company is currently operating in a period of macroeconomic uncertainty and capital markets disruption, which has been impacted by domestic and global monetary and fiscal policy, geopolitical instability, including ongoing military conflicts between Russia and Ukraine and in Israel and surrounding areas, rising tensions between China and Taiwan, a recessionary environment, historically high domestic and global inflation, high interest rates and instability in banks and other financial institutions. The Company's future results of operations and liquidity could be adversely impacted by outbreaks of disease, epidemics and pandemics, including potential further delays in existing and planned clinical trials, difficulty in recruiting patients for these clinical trials, delays in manufacturing and collaboration activities and supply chain disruptions. The conflict in Ukraine has exacerbated market disruptions, including significant volatility in commodity prices as well as supply chain interruptions, and has contributed to record inflation globally. The U.S. Federal Reserve and other central banks may be unable to contain inflation through more restrictive monetary policy and inflation may increase or continue for a prolonged period of time. Inflationary factors, such as increases in the cost of clinical supplies, interest rates, overhead costs and transportation costs may adversely affect the Company's operating results. In addition, the failure of Silicon Valley Bank and other regional banks in the United States during the first half of 2023 has given rise to uncertainty in the security of amounts in deposit accounts uninsured by the Federal Deposit Insurance Corporation. The Company continues to monitor these events and the potential impact on its business. Although the Company does not believe that inflation has had a material adverse impact on its financial position or results of operations to date, its financial position or results of operations may be adversely affected in the future due to numerous factors, including global monetary and fiscal policy, supply chain constraints, the ongoing conflicts between Russia and Ukraine and in Israel and surrounding areas and other factors, and such factors may lead to increases in the cost of manufacturing for and delays in the initiation of studies in the Company's product candidates.

Note 2. Summary of Significant Accounting Policies

Basis of Presentation and Consolidation

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

Effective January 1, 2023, the financial statements of Protagonist Australia use the U.S. dollar as the functional currency, which reflects the expected nature of the ongoing operations of this subsidiary. The cumulative translation adjustment as of January 1, 2023 related to this subsidiary was not material. Prior to January 1, 2023, the financial statements of Protagonist Australia used the Australian dollar as the functional currency since the majority of expense transactions occurred in such currency. 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.

There has been uncertainty and disruption in the global economy and financial markets due to a number of factors, including geopolitical instability, inflationary pressures, high interest rates, a recessionary environment, domestic and global monetary and fiscal policy and other factors. The Company has taken into consideration any known impacts in its accounting estimates to date and is not aware of any additional specific events or circumstances that would require any additional updates to its estimates or judgments or a revision of the carrying value of its assets or liabilities as of the filing date of this Annual Report on Form 10-K. These estimates may change as new events occur and additional information is obtained. Actual results could differ materially from these estimates under different assumptions or conditions.

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash, cash equivalents and marketable securities. Substantially all of the Company's cash is held by three financial institutions that management believes are of high credit quality. Such deposits generally 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.

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 Company's letter of credit balance was $0.2 million at December 31, 2021, 2022 and 2023 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,		
	2023	2022	2021
Cash and cash equivalents	$ 186,727	$ 125,744	$ 123,665
Restricted cash - noncurrent	225	225	225
Total cash reported on consolidated statements of cash flows	$ 186,952	$ 125,969	$ 123,890

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 income (loss). Realized gains and losses, if any, on available-for-sale securities are included in interest income. The cost of securities sold is based on the specific-identification method. Interest on marketable securities is included in interest income.

Fair Value of Financial Instruments

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

Investment Impairment

As of each reporting date, the Company assesses each of its investments in available-for-sale debt securities whose fair value is below its cost basis to determine if the investment's impairment is due to credit-related factors or noncredit-related factors. Factors considered in determining whether an impairment is credit-related include the extent to which the investment's fair value is less than its cost basis, declines in published credit ratings, issuer default on interest or principal payments, and declines in the financial condition and near-term prospects of the issuer. Credit-related impairments on available-for-sale debt securities are recognized as an allowance for credit losses with a corresponding adjustment to other

income (expense), net. The portion of the impairment that is not credit-related is recorded as a reduction of other comprehensive income (loss), net of applicable taxes.

Pursuant to Accounting Standard Update 2016-13, *Financial Instruments - Credit Losses (Topic 326)* ("ASU 2016-13"), the Company has elected to exclude accrued interest from both the fair value and the amortized cost basis of the available-for-sale debt securities for the purposes of identifying and measuring an impairment. The Company writes off accrued interest as a reduction of interest income when an issuer has defaulted on interest payments due on a security.

Property and Equipment

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

Leases

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

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

Impairment of Long-Lived Assets

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

Comprehensive Loss

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

Income Taxes

The Company uses the asset and liability method to account for income taxes in accordance with the authoritative guidance for income taxes. Under this method, deferred tax assets and liabilities are determined based on future tax

consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases, and tax loss and credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates applied to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in the period that includes the enactment date. A valuation allowance is established when necessary to reduce deferred tax assets to the amount expected to be realized.

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

Revenue Recognition

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

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

Milestone payments: At the inception of each arrangement or amendment that includes development, regulatory or commercial milestone payments, the Company evaluates whether the milestones are considered probable of being reached and estimates the amount to be included in the transaction price. ASC 606 suggests two alternatives to use when estimating the amount of variable consideration: the expected value method and the most likely amount method. Under the expected value method, an entity considers the sum of probability-weighted amounts in a range of possible consideration amounts. Under the most likely amount method, an entity considers the single most likely amount in a range of possible consideration amounts. Whichever method used should be consistently applied throughout the life of the contract; however, it is not necessary for the Company to use the same approach for all contracts. The Company expects to use the most likely amount method for development and regulatory milestone payments. If it is probable that a significant revenue reversal would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. If there is more than one performance obligation, the transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis. The Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each

subsequent reporting period, the Company re-evaluates the probability or achievement of each such milestone and any related constraint, and if necessary, adjusts its estimates of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

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

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

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

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

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

Research and Development Costs

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

The Company accrues for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of pre-clinical studies and clinical trials and contract manufacturing activities. The Company records the estimated costs of research and development activities based upon the estimated services provided but not yet invoiced and includes these costs in accrued expenses and other payables in the consolidated balance sheets and within research and development expense in the consolidated statements of operations. The Company accrues for these costs based on various factors such as estimates of the work completed and in accordance with agreements

established with its third-party service providers. As actual costs become known, the Company adjusts its accrued liabilities. The Company has not experienced any material differences between accrued liabilities and actual costs incurred. However, the status and timing of actual services performed, the number of patients enrolled, the rate of patient enrollment and the number and location of sites activated may vary from the Company's estimate and may result in adjustments to research and development expenses in future periods. Changes in these estimates that result in material changes to the Company's accruals could materially affect the Company's results of operations.

Research and Development Tax Incentive

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

Stock-based Compensation

The Company measures its stock-based awards made to its equity plan participants based on the estimated fair values of the awards as of the grant date. For stock option awards, the Company uses the Black-Scholes option-pricing model to estimate fair values. For restricted stock unit ("RSU") 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 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 on an accelerated basis over the vesting periods of the awards that are ultimately expected to vest when achievement of the related performance obligation becomes probable. The Company assesses the probability of achievement of the related performance obligation on a quarterly basis.

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, Exchange Warrants and Pre-Funded Warrants (as defined in Note 10. Stockholders' Equity for details) outstanding during the period, without consideration of potentially dilutive securities. In accordance with Accounting Standards Codification Topic 260, *Earnings Per Share* ("ASC 260"), outstanding Exchange Warrants and Pre-Funded 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 10. Stockholders' Equity for additional information regarding the Exchange Warrants and Pre-Funded Warrants.

Recently Adopted Accounting Pronouncements

In June 2016, the Financial Accounting Standard Board ("FASB") issued ASU 2016-13. The guidance requires measurement and recognition of expected credit losses for financial assets at the time financial assets are initially recognized in the financial statements. The measurement of expected credit losses is based on historical credit loss information as well as current and future economic factors. ASU 2016-13 also eliminates the concept of "other-than-temporary" impairment when evaluating available-for-sale debt securities and instead focuses on determining whether any impairment is a result of credit loss or other factors. In November 2019, the FASB issued Accounting Standards Update 2019-10, *Financial Instruments – Credit Losses (Topic 326): Effective Dates*, which delayed the mandatory effective date of ASU 2016-13 for smaller reporting companies. The Company adopted ASU 2016-13 effective January 1, 2023. The adoption of this guidance did not have a material impact on the Company's consolidated financial statements or related disclosures.

Recently Issued Accounting Pronouncements as of December 31, 2023

In December 2023, the FASB issued Accounting Standards Update No. 2023-09 *Income Taxes (Topic 740) – Improvements to Income Tax Disclosures* ("ASU 2023-09"), which requires public business entities to disclose specific categories in the income tax rate reconciliation annually and provide additional information for reconciling items that meet a qualitative threshold. ASU 2023-09 also requires that entities disclose annually additional information about income taxes paid and disaggregated information for certain items. ASU 2023-09 is effective for the Company beginning on January 1, 2025. The Company is currently evaluating the impact of the adoption of ASU 2023-09 on its financial position, results of operations and cash flows.

In November 2023, the FASB issued Accounting Standards Update No. 2023-07 *Segment Reporting (Topic 280) – Improvements to Reportable Segment Disclosures* ("ASU 2023-07"), which requires public entities to disclose incremental segment information on an annual and interim basis. ASU 2023-07 requires public entities with a single reportable segment to provide all the disclosures required by the amendments in ASU 2023-07 and all existing segment disclosures in *Segment Reporting (Topic 280)*. ASU 2023-07 is effective for the Company for fiscal years beginning on January 1, 2024, and interim periods within fiscal years beginning on January 1, 2025. The Company does not expect the adoption of ASU 2023-07 to have a material impact on its financial position, results of operations or cash flows.

In August 2020, the FASB issued Accounting Standards Update No. 2020-06, *Debt - Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging - Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity* ("ASU 2020-06"), which simplifies accounting for convertible instruments by removing major separation models required under current GAAP. ASU 2020-06 also removes certain settlement conditions that are required for equity-linked contracts to qualify for the derivative scope exception, and it simplifies the diluted earnings per share calculation in certain areas. ASU 2020-06 is effective for the Company beginning on January 1, 2024. The Company does not expect the adoption of ASU 2020-06 to have a material impact on its financial position, results of operations or cash flows.

Note 3. License and Collaboration Agreement

Agreement Terms

On July 27, 2021, the Company entered into an Amended and Restated License and Collaboration Agreement (the "Restated Agreement") with J&J Innovative Medicines ("JNJ"), formerly Janssen Biotech, Inc., which amended and restated the License and Collaboration Agreement, effective July 13, 2017, by and between the Company and JNJ (the "Original Agreement"), as amended by the first amendment, effective May 7, 2019 (the "First Amendment"). Prior to January 1, 2023, JNJ was a related party to the Company as Johnson & Johnson Innovation - JJDC, Inc. was a significant (greater than 5%) stockholder of the Company, and both companies are subsidiaries of Johnson & Johnson. Upon the effectiveness of the Original Agreement, the Company received a non-refundable, upfront cash payment of $50.0 million from JNJ. Upon the effectiveness of the First Amendment, the Company received a $25.0 million payment from JNJ in 2019. The Company received a $5.0 million payment triggered by the successful nomination of a second-generation oral Interleukin ("IL")-23 receptor antagonist development compound ("second-generation compound") during the first

quarter of 2020 and a $7.5 million payment triggered by the completion of data collection activities for the first Phase 1 clinical trial of a second-generation compound during the fourth quarter of 2021. The Company received a $25.0 million milestone payment in connection with the dosing of the third patient in the first Phase 2 clinical trial for a second-generation compound during the second quarter of 2022. The Company received a $50.0 million milestone payment in connection with the dosing of a third patient in the ICONIC-TOTAL Phase 3 clinical trial of JNJ-2113 in patients with moderate-to-severe psoriasis during the fourth quarter of 2023. The Company became eligible to receive a $10.0 million milestone payment upon the dosing of the third patient in the ANTHEM Phase 2b trial in UC in December 2023. The Company has earned a total of $172.5 million in non-refundable payments from JNJ since the inception of the Restated Agreement in 2017 through the date of this report.

The Restated Agreement relates to the development, manufacture and commercialization of oral IL-23 receptor antagonist drug candidates. The candidates nominated for initial development pursuant to the Restated Agreement included PTG-200 (JNJ-67864238), PN-232 (JNJ-75105186) and JNJ-2113 (JNJ-77242113) (formerly PN- 235). PTG-200 is an oral IL-23 receptor antagonist that was in Phase 2a development for the treatment of Crohn's disease ("CD"). During the fourth quarter of 2021, a decision was made by JNJ to stop further development of both PTG-200 and PN-232 in favor of advancing JNJ-2113, based on its superior potency and overall pharmacokinetic and pharmacodynamic profile. JNJ is primarily responsible for the conduct of all future trials, including anticipated Phase 2 and Phase 3 trials, and the Company is primarily responsible for the conduct of the second-generation Phase 1 trials.

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

Upcoming potential development milestones for second-generation compounds include:

- $115.0 million upon a Phase 3 clinical trial for a second-generation compound for any indication meeting its primary clinical endpoint;
- $35.0 million upon the filing of a New Drug Application ("NDA") for a second-generation compound with the U.S. Food and Drug Administration (the "FDA");
- $50.0 million upon FDA approval of an NDA for a second-generation compound; and
- $15.0 million upon the dosing of the third patient in a Phase 3 clinical trial for a second-generation compound for a second indication.

Pursuant to the Restated Agreement, the Company remains eligible to receive tiered royalties on net product sales at percentages ranging from six percent 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. JNJ bills the Company for its share of the PTG-200 Phase 2a development costs as expenses are incurred by JNJ. Milestone payments are received after the related milestones are achieved.

JNJ retains exclusive, worldwide rights to develop and commercialize IL-23 receptor antagonist compounds derived from the research collaboration conducted under the Original Agreement, or JNJ's further research under the Restated Agreement. Any further research and development will be conducted by JNJ. The Company will have the right to co-detail (for CD and ulcerative colitis ("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, JNJ would, if requested, provide certain financial and operational support to the Company for the completion of such trials.

Revenue Recognition

The Restated Agreement contains a single performance obligation for the development license; Phase 1 development services for PTG-200, PN-232 and JNJ-2113; 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 JNJ to support the development of PTG-200 through Phase 2a and PN-232 and JNJ-2113 through Phase 1. Under the Restated Agreement, development services performed by the Company for PTG-200 beyond Phase 2a and PN-232 and JNJ-2113 beyond Phase 1 are no longer required.

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

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

The Company uses the most likely amount method to estimate variable consideration included in the transaction price. Variable consideration after the effective date of the Restated Agreement consisted of future milestone payments and cost sharing payments for agreed-upon services offset by development costs reimbursable to JNJ. Cost sharing payments from JNJ related to the agreed-upon services for development activities that the Company performed within the duration of the contract were included in the transaction price at the Company's share of the estimated budgeted costs for these activities, including primarily internal full-time equivalent effort and third-party contract costs. Cost sharing payments to JNJ related to agreed-upon services for activities that JNJ performed within the duration of the contract are not a distinct service that JNJ transfers to the Company. Therefore, the consideration payable to JNJ was accounted for as a reduction in the transaction price.

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

The Company utilized a cost-based input method to measure proportional performance and to calculate the corresponding amount of revenue to recognize. In applying the cost-based input method of revenue recognition, the

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

For the year ended December 31, 2023, the Company recognized $60.0 million of license and collaboration revenue, which included a $50.0 million milestone payment earned in October 2023 in connection with the dosing of the third patient in the ICONIC-TOTAL Phase 3 trial of JNJ-2113 in patients with moderate-to-severe psoriasis, and a $10.0 million milestone payment earned in December 2023 upon the dosing of the third patient in the ANTHEM Phase 2b trial in UC.

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

For the year ended December 31, 2021, the Company recognized $27.4 million of license and collaboration revenue. This amount included a cumulative catch-up adjustment increasing license and collaboration revenue by $8.0 million, and $18.6 million of license and collaboration revenue based on proportional performance following the 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 Restated Agreement.

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

Year Ended December 31, 2023	Balance at Beginning of Period	Additions	Deductions	Balance at End of Period
Contract assets:				
Receivable from collaboration partner	$ 10	$ 60,041	(50,051)	$ 10,000
Contract liabilities:				
Payable to collaboration partner	$ 69	$ 11	(77)	$ 3

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

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

Note 4. Fair Value Measurements

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

a three-tiered hierarchy, which prioritizes the inputs used in the valuation methodologies in measuring fair value as follows:

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

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

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

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

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

	December 31, 2023			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$ 19,212	$ —	$ —	$ 19,212
Certificates of deposit	—	13,004	—	13,004
Commercial paper	—	130,296	—	130,296
Corporate debt securities	—	7,672	—	7,672
U.S. Treasury and agency securities	—	145,085	—	145,085
Total financial assets	$ 19,212	$ 296,057	$ —	$ 315,269

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

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

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

Note 5. Cash Equivalents and Marketable Securities

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

	December 31, 2023			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Money market funds	$ 19,212	$ —	$ —	$ 19,212
Certificates of deposit	12,998	6	—	13,004
Commercial paper	130,351	5	(60)	130,296
Corporate debt securities	7,678	—	(6)	7,672
U.S. Treasury and agency securities	145,024	63	(2)	145,085
Total cash equivalents and marketable securities	$ 315,263	$ 74	$ (68)	$ 315,269
Classified as:				
Cash equivalents				$ 160,379
Marketable securities				154,890
Total cash equivalents and marketable securities				$ 315,269

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

Marketable securities of $154.9 million and $111.6 million held as of December 31, 2023 and 2022, respectively, had contractual maturities of less than one year. The Company does not intend to sell its securities that are in an unrealized loss position, and it is not more likely than not that the Company will be required to sell its securities before recovery of their amortized cost basis, which may be at maturity. There were no material realized gains or realized losses on marketable securities for the periods presented. The Company evaluated securities with unrealized losses to determine whether such losses, if any, were due to credit-related factors and determined that there were no credit-related losses to be recognized as of December 31, 2023.

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,	
	2023	2022
Prepaid insurance	$ 1,410	$ 1,417
Prepaid clinical and research related expenses	649	$ 2,746
Prepaid licenses	529	489
Other prepaid expenses	1,040	1,018
Other receivable	332	42
Prepaid expenses and other current assets	$ 3,960	$ 5,712

Property and Equipment, Net

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

	December 31,	
	2023	2022
Laboratory equipment	$ 5,323	$ 4,817
Furniture and computer equipment	1,143	1,089
Leasehold improvements	963	913
Total property and equipment	7,429	6,819
Accumulated depreciation	(6,234)	(5,254)
Property and equipment, net	$ 1,195	$ 1,565

Depreciation expense for the years ended December 31, 2023, 2022 and 2021, was $977,000, $1,032,000 and $813,000, respectively. As of December 31, 2023, 2022 and 2021, $56,000, $156,000 and $262,000, respectively, of the Company's property and equipment, net, was located in Australia. The remainder of the Company's property and equipment, net was located in the United States.

Accrued Expenses and Other Payables

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

	December 31,	
	2023	2022
Accrued clinical and research related expenses	$ 11,841	$ 19,109
Accrued employee related expenses	6,786	4,967
Accrued professional service fees	632	464
Other	99	415
Total accrued expenses and other payables	$ 19,358	$ 24,955

Note 7. Research Collaboration and License Agreement

The Company and Zealand Pharma A/S ("Zealand") entered into a collaboration agreement in June 2012. In October 2013, Zealand 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. In August 2021, the Company and Zealand agreed to resolve the dispute and entered into an Arbitration Resolution Agreement.

See Note 9. Commitments and Contingencies – Legal Proceedings for additional information on the results of arbitration proceedings related to this research and collaboration agreement.

Milestone payments to collaboration partners are recorded as research and development expense in the period that the expense is incurred. For the year ended December 31, 2021, the Company recorded research and development

expense of $4.0 million under this agreement. No research and development expense were recorded under this agreement for the years ended December 31, 2023 or 2022.

Note 8. 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. In July 2021, the Company entered into a second amendment to its original facility lease agreement, as amended, for 15,000 square feet of additional office space in Newark, California (the "Second Amendment"). The Company commenced operations in the additional space in September 2021. Under the Second Amendment, the Company will pay additional base rent of approximately $1.5 million over the lease term, which expires in May 2024. As a result of this amendment, the Company recorded an additional right-of-use-asset and the related liability of $1.4 million as of December 31, 2021.

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

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

	December 31,	
Operating Leases:	**2023**	**2022**
Operating lease right-of-use asset	$ 954	$ 3,061
Operating lease liability - current	$ 1,141	$ 2,515
Operating lease liability - noncurrent	—	1,141
Total operating lease liabilities	$ 1,141	$ 3,656
Weighted-average remaining lease term (years)	0.4	1.4
Weighted-average discount rate	10.4%	10.4%

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

	Year Ended December 31,		
	2023	**2022**	**2021**
Operating lease cost	$ 2,335	$ 2,335	$ 1,962
Less: Sublease income	(137)	(123)	(91)
Total lease expense	$ 2,198	$ 2,212	$ 1,871

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

	Year Ended December 31,		
	2023	**2022**	**2021**
Operating cash flow used by operating leases	$ 2,743	$ 2,661	$ 2,049
New operating lease asset obtained in exchange for operating lease liability	$ —	$ —	$ 1,373

Future lease payments required under lease obligations as of December 31, 2023 are as follows (in thousands):

Year Ending December 31:	Amount
2024	$ 1,160
2025	—
2026	—
2027	—
Thereafter	—
Total future minimum lease payments	1,160
Less: imputed interest	(19)
Present value of lease liabilities	$ 1,141

Note 9. Commitments and Contingencies

Contract Service Providers

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

Indemnification Agreements

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

Legal Proceedings

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

In January 2020, the Company initiated arbitration proceedings with the International Court of Arbitration of the International Chamber of Commerce against 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.

In August, the Company and Zealand agreed to resolve the dispute and reached an Arbitration Resolution Agreement. Under the Arbitration Resolution Agreement, (1) the Company was required to make an additional payment of $1.5 million to Zealand in August 2022 with respect to rusfertide; (2) all development milestones with respect of rusfertide were reduced by 50%, except that the Company agreed to pay in full within two business days after the

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

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

Note 10. Stockholders' Equity

Public Offerings

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

In April 2023, the Company completed an underwritten public offering of 5,000,000 shares of its common stock at a public offering price of $20.00 per share and issued an additional 750,000 shares of common stock at a price of $20.00 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 $107.8 million.

ATM Offerings

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

In August 2022, the Company entered into an Open Market Sale Agreement℠ , pursuant to which the Company may offer and sell up to $100.0 million shares of its common stock from time to time in "at-the-market" offerings (the "2022 ATM Facility"). During the three months ended March 31, 2023, the Company sold 1,749,199 shares of its common stock under the 2022 ATM Facility for net proceeds of $24.3 million, after deducting issuance costs. There were no sales of the Company's common stock under the 2022 ATM Facility during the three months ended June 30, 2023, September 30, 2023 and December 30, 2023. There were no sales of the Company's common stock under the 2022 ATM Facility during the year ended December 31, 2022.

Exchange Warrants

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 expired ten years from the date of issuance. The Exchange Warrants were exercisable at any time prior to

expiration except that the Exchange Warrants could not be exercised by the Exchanging Stockholders if, after giving effect thereto, the Exchanging Stockholders would beneficially own more than 9.99% of the Company's common stock, subject to certain exceptions. In accordance with Accounting Standards Codification Topic 505, *Equity*, the Company recorded the retirement of the common stock exchanged as a reduction of common stock shares outstanding and a corresponding debit to additional paid-in-capital at the fair value of the Exchange Warrants on the issuance date. The Exchange Warrants met the criteria for equity classification and the fair value of the Exchange Warrants was recorded as a credit to additional paid-in capital and was not subject to remeasurement. The Company determined that the fair value of the Exchange Warrants was substantially similar to the fair value of the retired shares on the issuance date due to the negligible exercise price for the Exchange Warrants. During the year ended December 31, 2022, Exchange Warrants to purchase 400,000 shares of the Company's common stock were net exercised, resulting in the issuance of 399,997 shares of common stock. As of December 31, 2023, there were no outstanding Exchange Warrants.

Pre-Funded Warrants

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 was exercisable from August 8, 2018 through August 8, 2023. Warrants to purchase 1,375,000 shares of the Company's common stock had an exercise price of $10.00 per share and Warrants to purchase 1,375,000 shares of the Company's common stock had 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") were 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 were 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 met the criteria for equity classification and the net proceeds from the transaction were recorded as a credit to additional paid-in capital.

In August 2023, prior to the expiration of the Warrants, the Company entered into certain agreements with the Investors and their affiliates under which the Company agreed to allow the Warrants to be exercised in exchange for pre-funded warrants representing the same number of Warrant Shares underlying the Warrants with an exercise price of $0.001 per share (the "Pre-Funded Warrants"). Subsequent to the execution of the agreements and prior to the expiration of the Warrants, all outstanding Warrants were exercised for gross proceeds of $34.4 million in exchange for 44,748 shares of the Company's common stock and Pre-Funded Warrants to purchase 2,705,252 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 Pre-Funded Warrants) with an exercise price of $0.001 per share. The Pre-Funded Warrants will expire upon the day they are exercised in full. The Pre-Funded Warrants are exercisable at any time prior to expiration except that the Pre-Funded Warrants cannot be exercised by the Investors if, after giving effect thereto, the Investors would beneficially own more than 9.99% of the Company's common stock, subject to certain exceptions. The common stock and Pre-Funded Warrants met the criteria for equity classification and the net proceeds from the transaction were recorded as a credit to additional paid-in capital. In accordance with ASC 260, outstanding Pre-Funded 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. As of December 31, 2023, none of the Pre-Funded Warrants have been exercised.

Note 11. 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 members of the Company's Board of Directors

("Board") 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 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. 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, 2023, approximately 1,035,798 shares of common stock were available for issuance under the 2016 Plan.

The 2016 Plan is administered by the Board, or a committee appointed by 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. 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 Board director initial stock options generally vest monthly over a period of approximately three years, and non-employee Board director annual refresher stock options generally vest over a period of approximately one year. Consultant awards generally vest over a period of approximately one year.

Inducement Plan

In May 2018, the Company's Board approved the 2018 Inducement Plan, as subsequently amended. The 2018 Inducement Plan is a non-stockholder approved stock plan, under which awards options and restricted stock unit awards to persons that were not previously employees or directors of the Company, or following a bona fide period of non-employment, as an inducement material to such persons entering into employment with the Company, within the meaning of Rule 5635(c)(4) of the Nasdaq Listing Rules. The 2018 Inducement Plan is administered by the Board 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. Employee stock options granted under the 2018 Inducement Plan generally vest over a period of approximately four years. As of December 31, 2023, approximately 548,722 shares of common stock were available for issuance under the 2018 Inducement Plan, as amended.

Stock Options

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

	Options Outstanding	Weighted-Average Exercise Price Per Share	Weighted-Average Remaining Contractual Life (years)	Aggregate Intrinsic Value [1] (in millions)
Balances at December 31, 2022	6,240,509	$ 19.03		
Options granted	2,519,750	13.07		
Options exercised	(345,407)	11.04		
Options forfeited	(492,809)	23.48		
Balances at December 31, 2023	7,922,043	$ 17.21	6.81	$ 60.0
Options exercisable – December 31, 2023	5,082,646	$ 16.93	5.77	39.4
Options vested and expected to vest – December 31, 2023	7,922,043	$ 17.21	6.81	$ 60.0

[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, 2023. The calculation excludes options with an exercise price higher than the closing price of the Company's common stock on December 31, 2023.

The aggregate intrinsic value of options exercised was $3.3 million, $5.4 million and $10.5 million for the years ended December 31, 2023, 2022 and 2021, respectively.

During the years ended December 31, 2023, 2022 and 2021, the estimated weighted-average grant-date fair value of common stock underlying options granted was $10.81, $17.52 and $21.94 per share, respectively.

For the years ended December 31, 2023, 2022 and 2021, the aggregate fair value of stock options that vested during the year was $25.9 million, $23.3 million and $11.3 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,		
	2023	2022	2021
Expected term (in years)	5.27- 6.08	5.27- 6.08	5.27- 6.08
Expected volatility	105.7% - 110.1%	96.3% - 101.7%	87.4% - 95.2%
Risk-free interest rate	3.57% - 4.86%	1.64% - 4.23%	0.11% - 1.35%
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— Beginning January 1, 2023, the Company's expected volatility is estimated based upon the volatility of the Company's stock price over a period equal to the expected term of the stock option grants. For the year ended December 31, 2022, the Company's expected volatility was estimated based upon a mix of 25% of the average

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

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 the 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.

RSUs

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

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

	Number of Shares		Weighted Average Grant Date Fair Value
Unvested RSUs at December 31, 2022	637,436	$	19.29
Granted	415,775		12.58
Vested	(302,582)		14.28
Forfeited	(86,138)		18.88
Unvested RSUs at December 31, 2023	664,491	$	18.40

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

For the years ended December 31, 2023, 2022 and 2021, the aggregate fair value of RSUs that vested during the year was $5.9 million, $1.7 million and $0.8 million, respectively.

PSUs

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

	Number of Shares		Weighted Average Grant Date Fair Value
Unvested PSUs at December 31, 2022	199,500	$	14.59
Granted	—		—
Vested	(114,000)		8.76
Forfeited	(10,000)		8.76
Unvested PSUs at December 31, 2023	75,500	$	23.57

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 vest, if at all, upon certification by the Compensation Committee of the Board 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 market 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.

During the year ended December 31, 2023, the Compensation Committee of the Board certified the actual achievement of performance objectives related to certain PSUs. As a result, recipients earned a total of 114,000 shares of common stock. The total fair market value of PSUs at vest date during the year ended December 31, 2023 was $3.0 million. No PSUs vested during the years ended December 31, 2022 and 2021.

The total fair value of grant date fair value of unvested PSUs outstanding as of December 31, 2023 was $1.8 million. As of December 31, 2023, the achievement of the related performance objectives was deemed not probable and, accordingly, no stock-based compensation expense for unvested PSUs has been recognized as of December 31, 2023.

Employee Stock Purchase Plan

In July 2016, the Company's Board 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 and the Compensation Committee of the Board. 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.

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, 2023, a total of 95,388 shares of common stock were issued under the 2016 ESPP, and approximately 1,459,902 shares of common stock were available for issuance as of December 31, 2023.

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,		
	2023	2022	2021
Expected term (in years)	0.50	0.50	0.50
Expected volatility	82.6% - 128.2%	117.5% - 128.2%	50.9% - 69.7%
Risk-free interest rate	3.56% - 5.17%	0.75% - 3.56%	0.06%
Dividend yield	—	—	—

Stock-Based Compensation

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

	Year Ended December 31,		
	2023	2022	2021
Research and development	$ 17,061	$ 14,719	$ 8,996
General and administrative	12,232	9,483	7,399
Total stock-based compensation expense	$ 29,293	$ 24,202	$ 16,395

As of December 31, 2023, total unrecognized stock-based compensation expense was approximately $45.4 million, which the Company expects to recognize over a weighted-average period of approximately 2.5 years.

Note 12. 401(k) Plan

The Company has a retirement and savings plan under Section of 401(k) of Internal Revenue Code (the "401(k) Plan") covering all U.S. employees. The 401(k) Plan allows employees to make pre- and post-tax contributions up to the maximum allowable amount set by the Internal Revenue Service. The Company may make contributions to this plan at its discretion. The Company matched 50% of each employee's contribution up to a maximum of $4,000 for the years ended December 31, 2023 and 2022 and $3,500 for the year ended December 31, 2021, resulting in recognized expense of approximately $0.4 million for the year ended December 31, 2023 and $0.3 million for each of the years ended December 31, 2022 and 2021.

Note 13. Income Taxes

No income tax expense was recorded by the Company for the years ended December 31, 2023, 2022, and 2021.

The Company's effective income tax rate differed from the Company's federal statutory rate of 21%, primarily because its U.S. loss cannot be benefited due to the full valuation position and reduced by foreign taxes.

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

	Year Ended December 31,		
	2023	2022	2021
Domestic	$ (76,779)	$ (124,208)	$ (125,797)
Foreign	(2,176)	(3,185)	246
Total net loss before taxes	$ (78,955)	$ (127,393)	$ (125,551)

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

	Year Ended December 31,		
	2023	2022	2021
Current:			
Federal	$ —	$ —	$ —
State	—	—	—
Foreign	—	—	—
Total current tax expense	—	—	—
Deferred:			
Federal	—	—	—
State	—	—	—
Foreign	—	—	—
Total deferred tax expense	—	—	—
Total income tax expense	$ —	$ —	$ —

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

	Year Ended December 31,		
	2023	2022	2021
Federal statutory income tax rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal benefit	8.1	1.4	1.9
Research and development credits	8.5	5.9	4.3
Foreign tax rate difference	0.2	0.2	—
Change in valuation allowance	(34.4)	(25.8)	(28.0)
Other	(3.4)	(2.7)	0.8
Provision for income taxes	— %	— %	— %

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

	December 31,	
	2023	2022
Deferred tax assets:		
Net operating loss carryforwards	$ 70,469	$ 76,133
Depreciation	950	893
Accruals/other	12,202	8,304
Operating lease liability	265	769
Research and development and foreign credits	38,759	30,387
Section 174 capitalized R&D expenditure	43,841	22,296
Total deferred tax assets	166,486	138,782
Deferred tax liabilities:		
Operating right-of-use asset	(221)	(644)
Total deferred tax liabilities	(221)	(644)
Valuation allowance	(166,265)	(138,138)
Net deferred tax assets	$ —	$ —

ASC 740 requires that the tax benefit of net operating losses, temporary differences and credit carryforwards be recorded as an asset to the extent that management assesses that realization is “more likely than not.” Realization of the future tax benefits is dependent on the Company’s ability to generate sufficient taxable income within the carryforward period. Because of the Company’s recent history of operating losses, management believes that recognition of the deferred tax assets arising from the above-mentioned future tax benefits is currently not likely to be realized and, accordingly, has provided a valuation allowance. The valuation allowance increased by approximately $28.1 million, $34.2 million and $32.0 million during the years ended December 31, 2023, 2022 and 2021, 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, 2023. The Company has experienced ownership changes in the past and in the current year. The ownership changes will not result in a limitation that will materially reduce the total amount of net operating loss carryforwards and credits that can be utilized. Subsequent ownership changes may affect the limitation in future years.

As of December 31, 2023, the Company had $322.8 million of federal net operating loss carryforwards and $215.1 million of state net operating loss carryforwards. $52.3 million of the federal net operating loss carryforwards will begin to expire in 2036, if not utilized, and the remaining $270.5 million have no expiration date. The state net operating loss carryforwards will begin to expire in 2035, if not utilized.

As of December 31, 2023, the Company did not have any Australian tax loss carryforward.

As of December 31, 2023, the Company had $36.9 million of federal and $12.8 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, 2023, the Company had AUD 5.2 million ($3.5 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,		
	2023	2022	2021
Balance at beginning of year	$ 25,295	$ 33,159	$ 19,885
Decreases based on tax positions related to prior years	—	(10,779)	—
Increases based on tax positions related to current year	2,730	2,915	13,274
Balance at end of year	$ 28,025	$ 25,295	$ 33,159

At December 31, 2023, the Company had unrecognized tax benefits of $28.0 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 amount 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, 2023, 2022 and 2021.

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.

Protagonist Australia had an accumulated deficit at December 31, 2023 and, accordingly, no provision has been provided thereon for any unremitted earnings.

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

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

Tax Law Updates

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

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

Note 14. Net Loss per Share

As the Company had a net loss for the each of the years ended December 31, 2023, 2022 and 2021, 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,		
	2023	2022	2021
Numerator:			
Net loss	$ (78,955)	$ (127,393)	$ (125,551)
Denominator:			
Weighted-average shares used to compute net loss per common share, basic and diluted	56,763,559	49,042,232	46,322,910
Net loss per share, basic and diluted	$ (1.39)	$ (2.60)	$ (2.71)

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,		
	2023	2022	2021
Options to purchase common stock	7,922,043	6,240,509	5,890,540
Common stock warrants	—	2,750,000	2,750,000
Restricted stock units	664,491	637,436	405,972
Performance stock units	75,500	199,500	105,500
ESPP shares	41,147	72,598	18,055
Total	8,703,181	9,900,043	9,170,067

Note 15. Subsequent Event

In January 2024, the Company entered into a worldwide license and collaboration agreement for the development and commercialization of rusfertide with Takeda Pharmaceuticals USA, Inc. (“Takeda”), which is yet to become effective. Under the terms of the agreement, the Company expects to receive an upfront payment of $300 million and to be eligible to receive additional worldwide development, regulatory and commercial milestone payments of up to $330 million, as well as tiered royalties from 10% to 17% on ex-U.S. net sales. The Company expects to be responsible for research and development through the completion of the Phase 3 VERIFY trial and U.S. regulatory approval. Takeda is expected to have rights for ex-U.S. development and to be responsible for leading global commercialization activities. The Company and Takeda expect to also share equally in U.S. profits and losses (50% to the Company and 50% to Takeda).

Further details related to the agreement, including the Company’s right to opt-out of the 50:50 U.S. profit and loss sharing arrangement in exchange for enhanced economics, are available on the Current Report on Form 8-K filed by the Company on January 31, 2024 with the SEC. The effectiveness of the agreement is dependent on and subject to the termination or expiration of any applicable waiting periods under the Hart-Scott-Rodino Act.

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, 2023. 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, 2023 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, 2023.

Our independent registered public accounting firm, Ernst & Young LLP, has audited the financial statements included in the Annual Report and has issued a report on the effectiveness of our internal control over financial reporting as of December 31, 2023. The report of Ernst & Young LLP is included below.

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, 2023, 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, 2023, 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, 2023 and 2022, the related consolidated statements of operations, comprehensive loss, stockholders' equity and cash flows for each of the three years in the period ended December 31, 2023, and the related notes, and our report dated February 27, 2024 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

San Mateo, California
February 27, 2024

Item 9B. Other Information

b) Trading Plans

On November 10, 2023, William D. Waddill, a member of our Board, adopted a trading plan intended to satisfy Rule 10b5-1(c) to sell up to 36,975 shares of the Company's common stock through November 10, 2024, or such earlier date when all transactions under the trading plan are completed, subject to certain conditions. During the quarter ended December 31, 2023, none of our other Section 16 officers or directors adopted or terminated a Rule 10b5-1 trading arrangement or a non-Rule 10b5-1 trading arrangement, as such terms are defined under Item 408(a) of Regulation S-K.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not applicable.

PART III

Item 10. Directors, Executive Officers, and Corporate Governance

Except as set forth below, the information required by this item is incorporated herein by reference to information in our Definitive Proxy Statement on Schedule 14A relating to our 2024 Annual Meeting of Stockholders, which we expect to be filed with the SEC within 120 days of our fiscal year ended December 31, 2023 (the "Proxy Statement"), including under the headings "Election of Directors," "Executive Officers," "Information Regarding Committees of the Board of Directors" and, if applicable, "Delinquent Section 16(a) Reports."

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

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

Item 11. Executive Compensation

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

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

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

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

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

Item 14. Principal Accountant Fees and Services

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

PART IV

Item 15. Exhibits, Financial Statement Schedules

(a) The following documents are filed as part of this Annual Report on Form 10-K:

(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 or Furnished Herewith
		Form	SEC File No.	Exhibit	Filing Date	
3.1	Amended and Restated Certificate of Incorporation.	8-K	001-37852	3.1	8/16/2016	
3.2	Amended and Restated Bylaws.	S-1/A	333-212476	3.2(b)	8/1/2016	
4.1	Specimen stock certificate evidencing the shares of common stock.	S-1/A	333-212476	4.1	8/1/2016	
4.2	Description of Protagonist Therapeutics, Inc.'s Securities Registered Pursuant to Section 12 of the Exchange Act.					X
4.3	Form of Pre-Funded Warrant	10-Q	001-37852	10.1	11/2/2023	
10.1+	Protagonist Therapeutics, Inc. 2007 Stock Option and Incentive Plan, as amended and restated, and form of option agreement, exercise notice, joinder, and adoption agreement thereunder.	S-1	333-212476	10.1	7/11/2016	
10.2+	Protagonist Therapeutics, Inc. 2016 Equity Incentive Plan and forms of stock option grant notice, option agreement, notice of exercise, restricted stock unit grant notice and restricted stock unit agreement thereunder.	S-1/A	333-212476	10.2	8/1/2016	
10.3+	Protagonist Therapeutics, Inc. 2016 Employee Stock Purchase Plan.	S-1/A	333-212476	10.3	8/1/2016	
10.4+	Form of Indemnity Agreement for Directors and Officers.	S-1/A	333-212476	10.4	8/1/2016	
10.5+	Protagonist Therapeutics, Inc. Amended and Restated 2018 Inducement Plan, and forms of stock option grant notice, option agreement, restricted stock unit grant notice and restricted stock unit agreement thereunder.	S-8	333-263097	99.3	2/28/2022	
10.6	Lease, dated March 6, 2017, by and between the Registrant and BMR-Pacific Research Center LP.	10-K	001-37852	10.9	3/7/2017	
10.7+	Severance Agreement, dated August 1, 2016, by and between the Registrant and Dinesh Patel.	S-1/A	333-212476	10.9	8/1/2016	
10.8†	Research and Collaboration Agreement, dated June 16, 2012, by and among the Registrant, Protagonist Pty. Ltd. and Zealand Pharma A/S.	S-1	333-212476	10.17	7/11/2016	

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed or Furnished Herewith
		Form	SEC File No.	Exhibit	Filing Date	
10.9†	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	
10.10†	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	
10.11†	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	
10.12†	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	
10.13†	Abandonment Agreement, dated February 28, 2014, by and among the Registrant, Protagonist Pty. Ltd. and Zealand Pharma A/S.	S-1	333-212476	10.22	7/11/2016	
10.14	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	
10.15	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	
10.16	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	
10.17	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	
10.18+	Severance Agreement, dated March 14, 2019, by and among Protagonist Therapeutics, Inc. and Suneel Gupta, Ph.D.	10-Q	001-37852	10.4	5/8/2019	

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

Exhibit Number	Exhibit Description	Incorporation By Reference				Filed or Furnished Herewith
		Form	SEC File No.	Exhibit	Filing Date	
32.1*	Certification of Chief Executive Officer and Chief Financial Officer, as required by Rule 13a-14(b) or Rule 15d-14(b) and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
97.1	Compensation Recoupment ("Clawback") Policy, adopted by Protagonist Therapeutics Inc. November 23, 2023.					X
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL Document.					X
101.SCH	Inline XBRL Taxonomy Extension Schema Document.					X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.					X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.					X
101.LAB	Inline XBRL Taxonomy Extension Labels Linkbase Document.					X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.					X
104	Cover Page Interactive Data File – the cover page interactive data file does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document.					

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

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

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

Item 16. Form 10-K Summary

None.

SIGNATURES

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

PROTAGONIST THERAPEUTICS, INC.

Date: February 27, 2024

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

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Dinesh V. Patel and Asif Ali, and each of them, his or her 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 27, 2024
/s/ Asif Ali Asif Ali	Executive Vice President, Chief Financial Officer *(Principal Financial and Accounting Officer)*	February 27, 2024
/s/ Harold E. Selick, Ph.D. Harold E. Selick, Ph.D.	Chairman of the Board of Directors	February 27, 2024
/s/ Bryan Giraudo Bryan Giraudo	Director	February 27, 2024
/s/ Sarah O'Dowd Sarah O'Dowd	Director	February 27, 2024
/s/ Daniel N. Swisher, Jr. Daniel N. Swisher, Jr.	Director	February 27, 2024
/s/ William D. Waddill William D. Waddill	Director	February 27, 2024
/s/ Lewis T. Williams, M.D., Ph.D. Lewis T. Williams, M.D., Ph.D.	Director	February 27, 2024

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 our Charter, the Company is authorized to issue up to 90,000,000 shares of common stock, par value $0.00001 per share ("Common Stock"), and up to 10,000,000 shares of preferred stock, par value $0.00001 per share ("Preferred Stock").

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 our 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 our 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, holders of our 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 holders of any Preferred Stock then outstanding.

Rights and Preferences

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

Anti-Takeover Effects of Delaware Law, our Charter and our Bylaws

Some provisions of Delaware law, our Charter 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 the 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 Charter 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 Charter 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 Charter 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 owned, 15% or more of a corporation's voting stock. Generally, a "business combination" includes a merger, consolidation, asset or stock sale, other transaction resulting in an increase of interested stockholder's share of the stock of the corporation or any receipt by the interested stockholder of any financial benefit by or through the corporation. 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 Charter 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 Delaware General Corporation Law or our Charter or Bylaws; or (4) 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 Securities Exchange Act of 1934, as amended, or any other claim for which the U.S. federal courts have exclusive jurisdiction. Our Charter 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 Charter 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 Charter 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 Equiniti Trust Company, LLC. The transfer agent and registrar’s address is 48 Wall Street, Floor 23, New York, New York 10005. Telephone number is (800) 468-9716.

Exhibit 21.1

SUBSIDIARIES OF PROTAGONIST THERAPEUTICS, INC.

Subsidiary	Jurisdiction of Formation/Organization
Protagonist Pty Limited	Australia

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the Registration Statements on Form S-8 (No. 333-213120, No. 333-216532, No. 333-223500, No. 333-225294, No. 333-230213, No. 333-237066, No. 333-254090, No. 333-263097, and No 333-270573) and in the Registration Statements on Form S-3 (No. 333-227216 and No. 333-266595) of Protagonist Therapeutics, Inc. and in the related Prospectuses, as applicable, of our report dated February 27, 2024, 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, 2023.

/s/ Ernst & Young LLP

San Mateo, California
February 27, 2024

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 27, 2024

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, Asif Ali, 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/ Asif Ali

Date: February 27, 2024

Asif Ali
Executive Vice President, Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER AND CHIEF FINANCIAL OFFICER
Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

Pursuant to 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, we, Dinesh V. Patel, Chief Executive Officer of Protagonist Therapeutics, Inc. (the "Company"), and Asif Ali, 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 year ended December 31, 2023 (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 Securities Exchange Act of 1934, as amended; 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 27, 2024

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

/s/ Asif Ali

Date: February 27, 2024

Asif Ali
Executive Vice President, Chief Financial Officer

This certification accompanies the Form 10-K to which it relates, and is not deemed to be 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.

Exhibit 97.1

PROTAGONIST THERAPEUTICS, INC.

COMPENSATION RECOUPMENT (CLAWBACK) POLICY

(as adopted November 28, 2023)

Recoupment of Incentive-Based Compensation

It is the policy of Protagonist Therapeutics, Inc. (the "Company") that, in the event the Company is required to prepare an accounting restatement of the Company's financial statements due to material non-compliance with any financial reporting requirement under the federal securities laws (including any such correction that is material to the previously issued financial statements, or that would result in a material misstatement if the error were corrected in the current period or left uncorrected in the current period), the Company will recover on a reasonably prompt basis the amount of any Incentive-Based Compensation Received by a Covered Executive during the Recovery Period that exceeds the amount that otherwise would have been Received had it been determined based on the restated financial statements.

Policy Administration and Definitions

This Policy is administered by the Compensation Committee (the "Committee") of the Company's Board of Directors, subject to ratification by the independent members of the Board of Directors with respect to application of this Policy to the Company's Chief Executive Officer, and is intended to comply with, and as applicable to be administered and interpreted consistent with, and subject to the exceptions set forth in, Listing Standard 5608 adopted by The Nasdaq Stock Market to implement Rule 10D-1 under the Securities Exchange Act of 1934, as amended (collectively, "Rule 10D-1").

For purposes of this Policy:

"Incentive-Based Compensation" means any compensation granted, earned, or vested based in whole or in part on the Company's attainment of a financial reporting measure that was Received by a person (i) on or after October 2, 2023 and after the person began service as a Covered Executive, and (ii) who served as a Covered Executive at any time during the performance period for the Incentive-Based Compensation. A financial reporting measure is (i) any measure that is determined and presented in accordance with the accounting principles used in preparing the Company's financial statements and any measure derived wholly or in part from such a measure, and (ii) any measure based in whole or in part on the Company's stock price or total shareholder return.

Incentive-Based Compensation is deemed to be "Received" in the fiscal period during which the relevant financial reporting measure is attained, regardless of when the compensation is actually paid or awarded.

"Covered Executive" means any "executive officer" of the Company as defined under Rule 10D-1.

"Recovery Period" means the three completed fiscal years immediately preceding the date that the Company is required to prepare the accounting restatement described in this Policy, all as determined pursuant to Rule 10D-1, and any transition period of less than nine months that is within or immediately following such three fiscal years.

If the Committee determines the amount of Incentive-Based Compensation Received by a Covered Executive during a Recovery Period exceeds the amount that would have been Received if determined or calculated based on the Company's restated financial results, such excess amount of Incentive-Based Compensation shall be subject to recoupment by the Company pursuant to this Policy. For Incentive-Based Compensation based on stock price or total shareholder return, where the amount of erroneously awarded compensation is not subject to mathematical recalculation directly from the information in an accounting restatement, the Committee will determine the amount based on a reasonable estimate of the effect of the accounting restatement on the relevant stock price or total shareholder return. In all cases, the calculation of the excess amount of Incentive-Based Compensation to be recovered will be determined without regard to any taxes paid with respect to such compensation. The Company will maintain and will provide to The Nasdaq Stock Market documentation of all determinations and actions taken in complying with this Policy. Any determinations made by the Committee under this Policy shall be final and binding on all affected individuals.

The Company may effect any recovery pursuant to this Policy by requiring payment of such amount(s) to the Company, by set-off, by reducing future compensation, or by such other means or combination of means as the Committee determines to be appropriate. The Company need not recover the excess amount of Incentive-Based Compensation if and to the extent that the Committee determines that such recovery is impracticable, subject to and in accordance with any applicable exceptions under The NASDAQ Stock Market listing rules, and not required under Rule 10D-1, including if the Committee determines that the direct expense paid to a third party to assist in enforcing this Policy would exceed the amount to be recovered after making a reasonable attempt to recover such amounts. The Company is authorized to take appropriate steps to implement this Policy with respect to Incentive-Based Compensation arrangements with Covered Executives.

Any right of recoupment or recovery pursuant to this Policy is in addition to, and not in lieu of, any other remedies or rights of recoupment that may be available to the Company pursuant to the terms of any other policy, any employment agreement or plan or award terms, and any other legal remedies available to the Company; provided that the Company shall not recoup amounts pursuant to such other policy, terms or remedies to the extent it is recovered pursuant to this Policy. The Company shall not indemnify any Covered Executive against the loss of any Incentive-Based Compensation pursuant to this Policy.