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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-220314

PROSPECTUS SUPPLEMENT
(To Prospectus Dated October 5, 2017)

2,750,000 Shares



Common Stock

We are offering 2,750,000 shares of our common stock, par value \$0.00001 per share. In a concurrent private placement, we are also selling warrants to purchase an aggregate of 2,750,000 shares of our common stock (the "Warrants"). Each Warrant will be exercisable from the date of issuance of the common stock sold hereunder until the five-year anniversary of the date of issuance of common stock sold hereunder. 1,375,000 Warrants will have an exercise price of \$10.00 per share (the "Class A Warrants") and 1,375,000 of the Warrants will have an exercise price of \$15.00 per share (the "Class B Warrants"), in each case subject to adjustment. The Warrants and the shares of common stock issuable upon the exercise of the Warrants (the "Warrant Shares") are not being registered under the Securities Act of 1933, as amended (the "Securities Act"), pursuant to the registration statement of which this prospectus supplement and the accompanying base prospectus form a part nor are such Warrants and Warrant Shares being offered pursuant to such prospectus supplement and base prospectus. The Warrants are being offered under an exemption from the registration requirements of the Securities Act. The Warrants are not and will not be listed for trading on any national securities exchange. Each purchaser will be an "accredited investor" as such term is defined in Rule 501(a) under the Securities Act.

Our common stock is listed on The Nasdaq Global Market under the symbol "PTGX." On August 3, 2018, the last reported sale price of our common stock was \$7.01 per share.

We are an "emerging growth company" under applicable Securities and Exchange Commission rules and are eligible for reduced public company disclosure requirements. See "Prospectus Supplement Summary—Company Information."

Our business and an investment in our common stock involve significant risks. These risks are described under the caption "Risk Factors" beginning on page S-9 of this prospectus supplement and page 7 of the accompanying prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal offense.

Delivery of the shares of common stock will be made on or about August 8, 2018.

Prospectus Supplement dated August 7, 2018

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We have not authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectus that we have authorized for use in connection with this offering. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement, the accompanying prospectus, any free writing prospectus that we have authorized for use in connection with this offering, including the documents incorporated by reference herein or therein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled "Where You Can Find More Information" and "Incorporation of Certain Information by Reference" in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the

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accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

Except as otherwise indicated herein or as the context otherwise requires, references in this prospectus to "Protagonist," "the company," "we," "us," "our" and similar references refer to Protagonist Therapeutics, Inc., a corporation under the laws of the State of Delaware.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, you should read and consider carefully the more detailed information included or incorporated by reference in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering, including the factors described under the heading "Risk Factors" beginning on page S-9 of this prospectus supplement, as well as the information included in any free writing prospectus that we have authorized for use in connection with this offering.

Protagonist Therapeutics, Inc.

Overview

We are a clinical stage biopharmaceutical company with a proprietary technology platform that enables the discovery and development of novel constrained peptide-based drug candidates that address significant unmet medical needs. Our product candidates are designed to affect critical steps in the biological pathways of particular diseases, for example, by blocking protein-protein interactions. We believe our peptide-based approach has advantages over alternative approaches such as small molecules and antibodies. Our clinical stage product candidates PTG-100 and PTG-200 are oral drugs that block biological pathways currently targeted by marketed injectable antibody drugs and offer targeted delivery to the gastrointestinal ("GI") tissue compartment. We believe that, as compared to antibody drugs, these product candidates have the potential to provide improved safety due to minimal exposure in the blood, increased convenience and compliance due to oral delivery, and the opportunity for the earlier introduction of targeted therapy.

PTG-100, an oral, alpha-4-beta-7 integrin antagonist, is being developed for potential treatment of inflammatory bowel disease ("IBD"), a GI disease consisting primarily of ulcerative colitis ("UC"), and Crohn's disease ("CD"). Recent developments regarding our Phase 2b PROPEL study of PTG-100 for the treatment of patients with UC and our development plans for PTG-100 are discussed below under the caption "Recent Developments."

PTG-200 is a potential first-in-class oral Interleukin-23 receptor ("IL-23R") antagonist for the treatment of IBD. It is currently in a Phase 1 healthy volunteer clinical study that was initiated in Australia in the fourth quarter of 2017. The IL-12/23 pathway blockade is an approach that has been validated through a U.S. Food and Drug Administration ("FDA") approved injectable antibody drug. We have entered into a worldwide license and collaboration agreement with Janssen Biotech, Inc. ("Janssen"), a Johnson & Johnson company, to co-develop and co-detail PTG-200 for all indications, including IBD. See the section below titled "Janssen License and Collaboration Agreement" for additional information. In the second half of 2018, we expect to file an Investigational New Drug application ("IND") in the United States and other regulatory filings outside the United States to support a global Phase 2 study of PTG-200 in CD to be conducted in collaboration with Janssen.

Our novel peptides have potential applicability in a wide range of therapeutic areas in addition to GI diseases. We have applied our versatile platform outside of the GI disease areas and are developing PTG-300, an injectable hepcidin mimetic, for the potential treatment of anemia and iron overload in certain rare blood disorders, with an initial focus on beta-thalassemia. In the fourth quarter of 2017, we completed a successful Phase 1 study of PTG-300 in healthy volunteers which established pharmacodynamic-based clinical proof of concept. PTG-300 received an orphan drug designation from the FDA for the treatment of beta-thalassemia in March 2018. We completed discussions with U.S. and global regulatory agencies and filed an IND in the United States in the second quarter of 2018. We

plan other global regulatory submissions to support the initiation of a global Phase 2 study of PTG-300 in patients with beta-thalassemia in the fourth quarter of 2018.

In addition, we continue to use our peptide technology platform to discover product candidates against targets in disease areas with significant unmet medical needs. In 2018, we anticipate initiating IND-enabling studies for a fourth product candidate, an oral peptide targeting a GI condition other than IBD.

We have not generated any revenue from product sales and we do not currently have any products approved for commercialization. We have never been profitable and have incurred net losses in each year since inception and we do not anticipate that we will achieve sustained profitability in the near term. Our net loss was \$37.0 million, \$37.2 million and \$14.8 million for the years ended December 31, 2017, 2016 and 2015, respectively. As of December 31, 2017, we had an accumulated deficit of \$101.6 million. Substantially all of our net losses have resulted from costs incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We expect to continue to incur significant research, development and other expenses related to our ongoing operations and product development, including clinical development activities under the Janssen License and Collaboration Agreement, and as a result, we expect to continue to incur losses in the future as we continue our development of, and seek regulatory approval for, our product candidates.

Janssen License and Collaboration Agreement

On May 26, 2017, we and Janssen entered into an exclusive license and collaboration agreement (the "Janssen License and Collaboration Agreement") for the development, manufacture and commercialization of PTG-200 worldwide for the treatment of CD and UC. Janssen is a related party to us as Johnson & Johnson Innovation—JJDC, Inc., a significant shareholder of ours, and Janssen are both subsidiaries of Johnson and Johnson. The Janssen License and Collaboration Agreement became effective on July 13, 2017. Upon the effectiveness of the agreement, we became eligible for and received a non-refundable, upfront cash payment of \$50.0 million from Janssen.

Under the Janssen License and Collaboration Agreement, we granted to Janssen an exclusive worldwide license to develop, manufacture and commercialize PTG-200 and related IL-23R compounds for all indications, including CD and UC. We are responsible, at our own expense, for the conduct of the Phase 1 clinical trial for PTG-200 and Janssen will be responsible for the conduct of a potential Phase 2 clinical trial for PTG-200 in CD, including filing the Phase 2 IND. All such clinical trials will be conducted in accordance with a mutually agreed upon clinical development plan and budget. Development costs for the Phase 2 clinical trial will be shared between the parties on an 80%/20% basis, with Janssen assuming the larger share. Should Janssen elect to retain its license following completion of the Phase 2 clinical trial, it will be responsible, at its own expense, for the manufacture, continued development of, seeking regulatory approval for, and commercialization of PTG-200 worldwide. The parties' development activities under the Janssen License and Collaboration Agreement through the Phase 2 clinical trial will be overseen by a joint governance structure which will have equal representation by both parties unless both parties mutually agree to disband such structure or we have provided written notice to Janssen of our intention to disband and no longer participate in such structure.

We are eligible to receive a \$25.0 million payment upon filing of the Phase 2 IND. Following the conclusion of the planned Phase 2a portion of the Phase 2 clinical trial, if Janssen elects to maintain its license rights and continue the development of PTG-200 in the Phase 2b portion of such clinical trial (the "First Opt-in Election"), we would be eligible to receive a \$125.0 million payment. Following the conclusion of the planned Phase 2b portion of the Phase 2 clinical trial, if Janssen elects again to maintain its license rights (the "Second Opt-in Election"), we would be eligible to receive a

\$200.0 million payment. In addition to the opt-in fees, we are eligible to receive additional potential development, regulatory and sales milestone payments of up to an aggregate of \$590.0 million, and tiered royalties paid as a percentage of Janssen's worldwide net sales at rates ranging from ten to the mid-teens, with certain customary reductions under certain circumstances. If Janssen does not make either the First Opt-in Election or the Second Opt-in Election, the Janssen License and Collaboration Agreement will terminate. If Janssen does not make the Second Opt-in Election, or if at any time after the Second Opt-in Election, Janssen terminates the Janssen License and Collaboration Agreement, we would be obligated to pay Janssen a low single-digit royalty on worldwide net sales of PTG-200. We would also have an option to provide up to 30% of the required U.S. details for PTG-200 to prescribers, using our own sales force personnel, upon commercial launch in the United States. If such right is exercised, our detailing costs would be reimbursed by Janssen, at a mutually agreed upon cost per primary detailing equivalent.

The Janssen License and Collaboration Agreement contains customary representations, warranties and covenants by us and Janssen and includes an obligation by us not to develop or commercialize other compounds which also target IL-23R outside of the Janssen License and Collaboration Agreement until completion of the Phase 2b portion of the Phase 2 clinical trial. We and Janssen are required to indemnify the other party against all losses and expenses related to breaches of its representations, warranties and covenants under the Janssen License and Collaboration Agreement.

The Janssen License and Collaboration Agreement remains in effect until the royalty obligations cease following patent and regulatory expiry, unless terminated earlier. Either we or Janssen may terminate the Janssen License and Collaboration Agreement for uncured material breach. Janssen retains the right to terminate the Janssen License and Collaboration Agreement for convenience and without cause on written notice of a certain period to us. Upon a termination of the Janssen License and Collaboration Agreement, all rights revert back to us, and in certain circumstances, if such termination occurs during ongoing clinical trials, Janssen would, if requested, provide certain financial and operational support to us for the completion of such trials.

Recent Developments

On August 6, 2018, we announced results from an independent blinded re-analysis of the Phase 2b PROPEL study of PTG-100 for the treatment of patients with UC. No safety concerns were noted with PTG-100. The data from blinded endoscopy re-reads and a comprehensive data review provide signals of clinical efficacy and support further development of PTG-100.

In March 2018, we announced the discontinuation of the PROPEL study. This decision followed a planned interim analysis by an independent Data Monitoring Committee ("DMC") of unblinded efficacy and safety data from the first 65 evaluable patients from the ongoing 240 patient trial. The DMC reported that the interim analysis met pre-specified futility criteria on the primary endpoint of clinical remission, and as a result the study was discontinued. No safety concerns were noted in the analysis. The interim data revealed an unusually high placebo rate of clinical remission of 24%, approximately four times higher than historical norms for similar UC studies, that led to the futility decision and discontinuation of the trial. A re-read of the endoscopies by the CRO's subcontractor and a subsequent fully blinded re-read of the endoscopies by an independent third party, Robarts Clinical Trials ("Robarts"), confirmed that a subset of the initial endoscopy reads provided by the CRO were in error. If the re-read of endoscopy results had been utilized for the interim futility analysis, the trial would have continued. Results of the complete data set as read by Robarts are summarized below. In

addition, improvements observed in histological scores favoring PTG-100 over placebo correlate with the clinical remission and endoscopic response outcomes from the re-analysis.

<u>Treatment arm (n=83)</u>	<u>Clinical remission</u>	<u>Endoscopic response*</u>
Placebo (n=21)	1 (4.8%)	1 (4.8%)
150 mg (n=22)	2 (9.1%)	2 (9.1%)
300 mg (n=21)	2 (9.5%)	3 (14.3%)
900 mg (n=19)	3 (15.8%)	3 (15.8%)

* defined as an endoscopic subscore of 0 or 1

We plan to meet with the FDA in the second half of 2018 to discuss next steps with regards to the Phase 2b clinical trial of PTG-100.

Company Information

Protagonist Pty Limited (Protagonist Australia) was incorporated in Australia in September 2001. We were incorporated under the laws of the State of Delaware in 2006, under the name Protagonist Therapeutics, Inc., and became the parent of Protagonist Australia pursuant to a transaction in which all of the issued and outstanding capital stock of Protagonist Australia was exchanged for shares of our common stock and Series A preferred stock. Our principal executive offices are located at 7707 Gateway Boulevard, Suite 140, Newark, California 94560. Our telephone number is (510) 474-0170. Our website address is www.protagonist-inc.com. The information contained in, or accessible through, our website does not constitute part of this prospectus, should not be relied on in determining whether to make an investment decision, and the inclusion of our website address in this prospectus is an inactive textual reference only.

The Protagonist logo and other trademarks or service marks of Protagonist Therapeutics, Inc. appearing in this prospectus are the property of Protagonist Therapeutics, Inc. Other trademarks, service marks or trade names appearing in this prospectus are the property of their respective owners. We do not intend our use or display of other companies' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

In addition, we are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act, or the JOBS Act, enacted in April 2012, and therefore we intend to take advantage of certain exemptions from various public company reporting requirements, including not being required to have our internal control over financial reporting audited by our independent registered public accounting firm pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and any golden parachute payments not previously approved.

We will remain an emerging growth company until the earlier of (1) December 31, 2021, (2) the last day of the fiscal year (a) in which we have total annual gross revenue of at least \$1.07 billion or (b) in which we are deemed to be a large accelerated filer, which means the market value of our common stock that is held by non-affiliates exceeds \$700 million as of the prior June 30th, and (3) the date on which we have issued more than \$1.0 billion in non-convertible debt securities during the prior three-year period.

THE OFFERING

Common Stock offered by us	2,750,000 shares.
Common Stock to be outstanding after this offering	23,913,590 shares.
Use of Proceeds	We currently intend to use the net proceeds from this offering to fund clinical research and development of PTG-100, including to potentially re-start the Phase 2b clinical trial of PTG-100. See "Use of Proceeds" on page S-15 of this prospectus supplement.
Risk Factors	You should carefully read and consider the information beginning on page S-9 of this prospectus supplement and page 7 of the accompanying prospectus set forth under the headings "Risk Factors" and all other information set forth in this prospectus supplement, the accompanying prospectus, and the documents incorporated herein and therein by reference before deciding to invest in our common stock and warrants.
The Nasdaq Global Market Symbol	Our shares are listed on The Nasdaq Global Market under the symbol "PTGX."

The number of shares of our common stock to be outstanding after this offering is based on 21,163,590 shares of our common stock outstanding as of March 31, 2018 and excludes:

- 2,984,522 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2018, having weighted average exercise price of \$12.67 per share;
- an aggregate of 664,068 shares of common stock, subject to increase on an annual basis, reserved for future issuance under our 2016 Equity Incentive Plan as of March 31, 2018;
- 113,625 shares issuable upon vesting of outstanding restricted stock units, or RSUs; and
- 454,660 shares of our common stock, subject to increase on an annual basis, reserved for future issuance under our 2016 Employee Stock Purchase Plan, as of March 31, 2018.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise of outstanding options or warrants after March 31, 2018.

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before you decide to invest in our common stock, you should carefully consider the risks and uncertainties described below and the risk factors incorporated by reference to our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety, together with all other information contained in this prospectus supplement, the accompanying prospectus and any free writing prospectus that we have authorized for use in connection with this offering, and in our filings with the SEC that we have incorporated by reference in this prospectus supplement and the accompanying prospectus. If any of such risks actually occurs, our business, prospects, operating results and financial condition could suffer materially. In such event, the trading price of our common stock could decline and you might lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business.

Risks Related to This Offering

Management will have broad discretion as to the use of the proceeds from this offering, and may not use the proceeds effectively.

Because we have not designated the amount of net proceeds from this offering to be used for any particular purpose, our management will have broad discretion as to the application of the net proceeds from this offering and could use them for purposes other than those contemplated at the time of the offering. Our management may use the net proceeds for corporate purposes that may not improve our financial condition or market value.

Investors in this offering will experience immediate and substantial dilution.

Since the price per share of our common stock being offered is substantially higher than the net tangible book value per share of our common stock, you will suffer immediate and substantial dilution in the net tangible book value of the common stock you purchase in this offering. Based on a public offering price of \$8.00 per share, if you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of \$2.30 per share with respect to the net tangible book value of the common stock. See the section entitled "Dilution" below for a more detailed discussion of the dilution you will incur if you purchase common stock in this offering.

There is uncertainty regarding the application of the federal and state securities laws to our offering of common stock and Warrants, and there is a corresponding risk that we could be required to refund the purchase price of securities offered to purchasers who so elect.

We are conducting an offering under a registration statement filed with the Securities and Exchange Commission and a concurrent private placement intended to comply with the requirements of Section 4(a)(2) under the Securities Act of 1933, as amended, and Rule 506(b) promulgated thereunder. See "Private Placement Transaction." Shares of common stock and Warrants are being offering and sold in combination. The shares of common stock are intended to be offered and sold in a transaction registered under the Securities Act, while the other Warrants and shares of common stock issuable thereunder are intended to be offered and sold in a private placement exempt from the registration requirements of the Securities Act.

While we are aware of other transactions using a concurrent public/private offering approach, the Commission has not addressed whether concurrent public and private offerings and sales to the same prospective investors would adversely impact the public offering or preclude the private offering from satisfying the requirements of Rule 506(b). If the securities offered in our concurrent private placement do not satisfy the conditions of Rule 506(b), the offering would be a violation of Section 5 of the

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Securities Act and each purchaser would have the right to rescind its purchase of the securities, meaning that we would be required to refund the purchase price of the securities to each purchaser electing rescission. If that were to occur, we would face severe financial demands and reputational harm that could adversely affect our business and operations. Additionally, if we did not in fact qualify for the exemptions upon which it has relied, we may become subject to significant fines and penalties imposed by the Commission. It is also possible that additional remedies may be available to purchasers under applicable state law.

Additional Risks Related to our Business

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

We are an early clinical-stage biopharmaceutical company with a limited operating history. 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, PTG-100, PTG-200 and PTG-300, and conducting research to identify additional product candidates. We successfully filed Clinical Trial Notifications in Australia to support our completed Phase 1 clinical trials of PTG-100, PTG-300 and our ongoing Phase 1 clinical trial of PTG-200. We successfully filed a U.S. IND application, and regulatory submissions in other countries as well, to support our global Phase 2b study of PTG-100 in ulcerative colitis ("UC"), however in March 2018 we announced that we were discontinuing this Phase 2b study following a planned interim analysis by an independent Data Monitoring Committee ("DMC") of unblinded efficacy and safety data from the first 65 evaluable patients from the ongoing 240 patient trial. Using pre-specified criteria, the DMC deemed the trial to be futile based on an analysis of the primary endpoint of clinical remission. In August 2018, we announced results from an independent blinded re-analysis of the data from the Phase 2b study. A signal of clinical efficacy with PTG-100 treatment was observed. We plan to discuss development with the FDA in the second half of 2018. Blinded re-analysis of initial interim data received from contract research organization identifies human error in initial endoscopy reads.

As an early clinical-stage company, we have not yet demonstrated an ability to generate revenue or successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields such as biopharmaceutical drug discovery and development. 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, but not limited to:

- the clinical outcomes from the continued development of our product candidates;
- potential side effects of our product candidates that could delay or prevent approval or cause an approved drug to be taken off the market;
- our ability to obtain, as well as the timeliness of obtaining, additional funding to develop and potentially manufacture and commercialize our product candidates, including payments, if any, under the Janssen License and Collaboration Agreement;
- competition from existing products directed against the same biological target or therapeutic indications of our product candidates as well as new products that may receive marketing approval;
- the entry of generic versions of products that compete with our product candidates;

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- the timing of regulatory review and approval of our product candidates;
- market acceptance of our product candidates that receive regulatory approval, if any;
- our ability to establish an effective sales and marketing infrastructure directly or through collaborations with third parties;
- the ability of patients or healthcare providers to obtain coverage or sufficient reimbursement for our products;
- the ability of third party manufacturers to manufacture in accordance with current good manufacturing practices our product candidates for the conduct of clinical trials and, if approved, for successful commercialization;
- our ability as well as the ability of any third-party collaborators, to obtain, maintain and protect intellectual property rights covering our product candidates and technologies, and our ability to develop, manufacture and commercialize our product candidates without infringing on the intellectual property rights of others;
- our ability to add infrastructure and manage adequately our future growth; and
- our ability to attract and retain key personnel with appropriate expertise and experience to manage our business effectively.

Accordingly, the likelihood of our success must be evaluated in light of many potential challenges and variables associated with an early 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 lead product candidates, PTG-100, PTG-200 and PTG-300, which are in early-stage clinical development, and if any of these products fail to receive regulatory approval or are not successfully commercialized, our business would be adversely affected.

We currently have no product candidates that are in registrational or pivotal clinical trials or are approved for commercial sale, and we may never be able to 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 lead product candidates, PTG-100 and PTG-200 targeting inflammatory bowel disease and PTG-300 which targets anemia associated with certain rare blood disorders, and the development of other product candidates. We cannot be certain that PTG-100, PTG-200, PTG-300 or any other product candidates will receive regulatory approval or, if approved, be successfully commercialized. The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of PTG-100, PTG-200, and PTG-300 will remain subject to extensive regulation by the FDA and other regulatory authorities in the United States and other countries, each of which has differing regulations. In addition, even if approved, our pricing and reimbursement will be subject to further review and discussions with payors. We are not permitted to market any product candidate in the United States until after approval of a new drug application ("NDA") from the FDA, or in any foreign countries until after approval of a marketing application by corresponding regulatory authorities. We completed a Phase 1 clinical trial for PTG-100 in June 2016 and initiated a global Phase 2b clinical trial of PTG-100 in patients with moderate to severe UC. In March 2018, we announced that we were discontinuing the global Phase 2b clinical trial for the treatment of moderate-to-severe UC. This decision followed a planned interim analysis by an independent DMC of unblinded efficacy and safety data from the first 65 evaluable patients from the ongoing 240 patient trial. Using pre-specified criteria, the DMC deemed the trial to be futile based on an analysis of the primary endpoint of clinical remission, and as a result the study was discontinued. In August 2018, we announced that results from an independent blinded re-analysis of the data from the Phase 2b study. A signal of clinical efficacy with PTG-100 treatment

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was observed. We plan to discuss development with the FDA in the second half of 2018. Blinded re-analysis of initial interim data received from contract research organization identifies human error in initial endoscopy reads. We also completed a Phase 1 clinical trial for PTG-300 in December 2017 and initiated a Phase 1 clinical trial of PTG-200 in November 2017. We will need to conduct larger, more extensive clinical trials in the target patient populations to support a potential application for regulatory approval by the FDA or corresponding regulatory authorities, and we do not expect to be in a position to do so for the near term. We may not receive any preferential or expedited review of any application for regulatory approval by virtue of the fact that our product candidates target biological pathways that are also targeted by currently marketed injectable antibody drugs, and our product candidates will be subject to the regulatory review processes applicable to completely new drugs.

We have not previously submitted an NDA to the FDA, or similar drug approval filings to comparable foreign authorities, for any product candidate, and we cannot be certain that any of our product candidates will be successful in clinical trial or receive regulatory approval. Filing an application and obtaining regulatory approval for a pharmaceutical product candidate is an extensive, lengthy, expensive and inherently uncertain process, and the regulatory authorities may delay, limit or deny approval of our product candidates for many reasons, including:

- we may not be able to demonstrate that any of our product candidates are safe and effective to the satisfaction of the FDA or comparable foreign regulatory authorities;
- the FDA or comparable foreign regulatory authorities may require additional pre-clinical studies or clinical trials prior to granting approval, which would increase our costs and extend the pre-approval development process;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA or comparable foreign regulatory authorities for approval;
- the FDA may disagree with the number, design, size, conduct or statistical analysis of one or more of our clinical trials;
- contract research organizations that we retain to conduct clinical trials may take actions outside of our control that materially and adversely impact our clinical trials;
- the FDA or comparable foreign regulatory authorities may disagree with, or not accept, our interpretation of data from our pre-clinical studies and clinical trials;
- the FDA may require development of a costly and extensive risk evaluation and mitigation strategy, as a condition of approval;
- the FDA or other regulatory authorities may require post-marketing studies as a condition of approval;
- the FDA may identify deficiencies in our manufacturing processes or facilities or those of our third-party manufacturers which would be required to be corrected prior to regulatory approval;
- the success or further approval of competitor products approved in indications in which we undertake development of our product candidates may change the standard of care or change the standard for approval of our product candidate in our proposed indications; and
- the FDA or comparable foreign regulatory authorities may change their approval policies or adopt new regulations.

Our peptide-based product candidates will require additional research, clinical development, manufacturing activities, regulatory approval in multiple jurisdictions (if regulatory approval can be obtained at all), securing sources of commercial manufacturing supply and building of or partnering with a commercial organization. We cannot assure you that our clinical trials for PTG-100, PTG-200 or

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PTG-300 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 peptide-based product candidates into clinical trials. Moreover, any delay or setback in the development of any product candidate, in particular PTG-100, PTG-200, or PTG-300, would be expected to adversely affect our business and cause our stock price to fall. For example, the announcement of the discontinuation of the global Phase 2b clinical trial of PTG-100 for the treatment of moderate-to-severe UC due to the interim analysis meeting the futility criterion on the primary endpoint of clinical remission significantly depressed our stock price.

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus, the documents incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering contain forward-looking statements, including statements regarding our future financial condition, business strategy and plans and objectives of management for future operations. Forward-looking statements include all statements that are not historical facts. In some cases, you can identify forward-looking statements by terminology such as "believe," "will," "may," "estimate," "continue," "anticipate," "intend," "should," "plan," "might," "approximately," "expect," "predict," "could," "potentially" or the negative of these terms or other similar expressions. Forward-looking statements appear in a number of places throughout this prospectus supplement, the accompanying prospectus, the documents incorporated by reference and any free writing prospectus that we have authorized for use in connection with this offering and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, the potential for our programs, the timing of our clinical trials, the potential for eventual regulatory approval and commercialization of our product candidates and our potential receipt of milestone payments and royalties under our collaboration agreement with Janssen, the potential outcome of any litigation or proceeding, future operating results or the ability to generate sales, income or cash flow are forward-looking statements.

Discussions containing these forward-looking statements may be found, among other places, in the section of this prospectus supplement under the heading "Risk Factors" and in the sections entitled "Business" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q, as well as any amendments thereto, filed with SEC. These statements relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that could cause our actual results, levels of activity, performance or achievement to differ materially from those expressed or implied by these forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these risks and uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the heading "Risk Factors" in this prospectus supplement and in the document incorporated by reference herein, and elsewhere in this prospectus supplement. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement and, except as required by law, we undertake no obligation to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus, 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.

USE OF PROCEEDS

We estimate that the net proceeds to us from our issuance and sale of shares of common stock in this offering will be approximately \$21.8 million, after deducting estimated offering expenses payable by us.

As of March 31, 2018, we had cash and cash equivalents and available for sale securities of \$140.5 million. We currently intend to use the net proceeds from the sale of the shares of our securities offered by us hereunder, if any, to fund clinical research and development of PTG-100.

The expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures depend on numerous factors, including the progress of our preclinical development efforts, the ongoing status of and results of our clinical trials and other studies and any unforeseen cash needs. As a result, our management will have broad discretion in the application of the net proceeds, and investors will be relying on the judgment of our management regarding the application of the net proceeds of this offering. Although we may use a portion of the net proceeds from the offering for the acquisition or licensing, as the case may be, of product candidates, technologies, compounds, other assets or complementary businesses, we have no current understandings, agreements or commitments to do so. Pending these uses, we intend to invest the net proceeds from this offering in interest-bearing, investment-grade securities.

Although it is difficult to predict future liquidity requirements, we believe that the net proceeds from this offering, together with our existing cash and cash equivalents will fund our operations for at least the next 12 months. However, circumstances may cause us to consume capital more rapidly than we anticipate.

DIVIDEND POLICY

We have never declared or paid, and do not anticipate declaring or paying in the foreseeable future, any cash dividends on our capital stock. Future determinations as to the declaration and payment of dividends, if any, will be at the discretion of our board of directors and will depend on then existing conditions, including our operating results, financial conditions, contractual restrictions, capital requirements, business prospects and other factors our board of directors may deem relevant.

CAPITALIZATION

The following table sets forth our cash and cash equivalents and our capitalization as of March 31, 2018 on:

- an actual basis; and
- an as adjusted basis to give effect to the assumed issuance and sale by us of 2,750,000 shares of common stock in this offering at a price of \$8.00 per share, after deducting estimated offering expenses payable by us.

The following information should be read in conjunction with the consolidated financial statements and related notes incorporated by reference in this prospectus supplement and the accompanying prospectus. For more details on how you can obtain the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, see "Where You Can Find More Information" and "Incorporation of Certain Information by Reference."

	As of	
	March 31, 2018	
	Actual	As Adjusted
	(in thousands, except share and per share data)	
Cash and cash equivalents	\$ 69,577	\$ 91,377
Stockholders' equity:		
Common stock, \$0.00001 par value—authorized, 90,000,000 actual and as adjusted; issued and outstanding, 21,163,590 actual and 23,913,590 as adjusted	—	—
Additional paid-in capital	223,904	245,704
Accumulated other comprehensive loss	(72)	(72)
Accumulated deficit	(109,211)	(109,211)
Total stockholders' equity	114,621	136,421
Total capitalization	\$ 114,621	\$ 136,421

The number of shares of our common stock to be outstanding after this offering is based on 21,163,590 shares of our common stock outstanding as of March 31, 2018 and excludes:

- 2,984,522 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2018, having weighted average exercise price of \$12.67 per share;
- an aggregate of 664,068 shares of common stock, subject to increase on an annual basis, reserved for future issuance under our 2016 Equity Incentive Plan as of March 31, 2018;
- 113,625 shares issuable upon vesting of outstanding restricted stock units, or RSUs; and
- 454,660 shares of our common stock, subject to increase on an annual basis, reserved for future issuance under our 2016 Employee Stock Purchase Plan, as of March 31, 2018.

DILUTION

Our net tangible book value as of March 31, 2018 was approximately \$114.6 million, or \$5.42 per share. Net tangible book value per share is determined by dividing our total tangible assets, less total liabilities, by the number of shares of our common stock outstanding as of March 31, 2018. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchasers of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

After giving effect to the assumed issuance and sale of shares of our common stock in this offering at an offering price of \$8.00 per share, and after deducting estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2018 would have been approximately \$136.4 million, or \$5.70 per share. This represents an immediate increase in net tangible book value of \$0.29 per share to existing stockholders and immediate dilution of \$2.30 per share to investors purchasing our common stock in this offering at the public offering price. The following table illustrates this dilution on a per share basis:

Offering Price per share	\$ 8.00
Net tangible book value per share of as March 31, 2018	\$ 5.42
Increase in net tangible book value per share attributable to this offering	\$ 0.29
As adjusted net tangible book value per share as of March 31, 2018, after giving effect to this offering	\$ 5.70
Dilution per share to new investors purchasing our common stock in this offering	\$ 2.30

The number of shares of our common stock to be outstanding after this offering is based on 21,163,590 shares of our common stock outstanding as of March 31, 2018 and excludes:

- 2,984,522 shares of common stock issuable upon the exercise of stock options outstanding as of March 31, 2018, having weighted average exercise price of \$12.67 per share;
- an aggregate of 664,068 shares of common stock, subject to increase on an annual basis, reserved for future issuance under our 2016 Equity Incentive Plan as of March 31, 2018;
- 113,625 shares issuable upon vesting of outstanding restricted stock units, or RSUs; and
- 454,660 shares of our common stock, subject to increase on an annual basis, reserved for future issuance under our 2016 Employee Stock Purchase Plan, as of March 31, 2018.

To the extent that options outstanding as of March 31, 2018 have been or may be exercised or other shares issued, investors purchasing our common stock in this offering may experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

PRIVATE PLACEMENT TRANSACTION

In a concurrent private placement (the "Private Placement Transaction"), we are selling to purchasers of our Common Stock in this offering one Class A Warrant and one Class B Warrant for each share purchased for cash in this offering. The aggregate number of shares common stock exercisable pursuant to the Class A Warrants is 1,375,000 and the aggregate number of shares common stock exercisable pursuant to the Class B Warrants is 1,375,000, in each case subject to adjustment.

The Warrants and the shares of our Common Stock issuable upon the exercise of the Warrants are not being registered under the Securities Act, are not being offered pursuant to this prospectus supplement and the accompanying prospectus and are being offered pursuant to the exemption provided in Section 4(a)(2) under the Securities Act and Rule 506(b) promulgated thereunder. Accordingly, purchasers may only sell shares of Common Stock issued upon exercise of the Warrants pursuant to an effective registration statement under the Securities Act covering the resale of those shares, an exemption under Rule 144 under the Securities Act or another applicable exemption under the Securities Act.

Each Warrant will be exercisable from the date of issuance of the common stock sold hereunder until the five-year anniversary of the date of issuance of common stock sold hereunder. The Warrants will be exercisable, at the option of each holder, in whole or in part by delivering to us a duly executed exercise notice and by payment in full in immediately available funds for the number of shares of common stock purchased upon such exercise. If a registration statement registering the issuance of the shares of common stock underlying the Warrants under the Securities Act is not then effective or available, the holder may exercise the Warrant through a cashless exercise, in whole or in part, in which case the holder would receive upon such exercise the net number of shares of common stock determined according to the formula set forth in the Warrant. No fractional shares of common stock will be issued in connection with the exercise of a Warrant. In lieu of fractional shares, we will either pay the holder an amount in cash equal to the fractional amount multiplied by the exercise price or round up to the next whole share.

The initial exercise price per share of common stock purchasable upon exercise of the Class A Warrants is \$10.00 per share of common stock. The initial exercise price per share of common stock purchasable upon exercise of the Class B Warrants is \$15.00 per share of common stock. In each case, the exercise price is subject to appropriate adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting our common stock.

In the event of a fundamental transaction, as described in the Warrants and generally including any reorganization, recapitalization or reclassification of our common stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the holders of the Warrants will be entitled to receive upon exercise of the Warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the Warrants immediately prior to such fundamental transaction.

PLAN OF DISTRIBUTION

We have entered into a securities purchase agreement with investors pursuant to which we will sell to such purchasers 2,750,000 shares of our common stock. The shares of common stock and Warrants will be issued separately but can only be purchased together in this offering. We negotiated the prices of the securities offered in this offering with the investors. The factors considered in determining the price included the recent market price of our common stock, the general condition of the securities market at the time of this offering, the history of, and the prospects for, the industry in which we compete, our past and present operations, and our prospects for future revenues.

The securities purchase agreement contains customary representations, warranties and covenants for transactions of this type. We have also agreed to indemnify the investors against certain losses resulting from our breach of any of our representations, warranties, or covenants under agreements with the purchasers as well as under certain other circumstances described in the securities purchase agreement.

We will deliver the shares of common stock being issued to the investors electronically upon receipt of investor funds for the purchase of the shares of our common stock offered pursuant to this prospectus supplement. We currently anticipate that the closing of the sale of the shares of common stock offered pursuant to this prospectus supplement will take place, and we expect to deliver the shares of our common stock that are purchased, on or about August 8, 2018. The obligations of the investors to close this offering are subject to certain conditions, including the absence of any material adverse change in our business.

We estimate the total offering expenses of this offering that will be payable by us will be approximately \$200,000, which include legal and printing costs and various other fees (and include the reimbursement of the purchasers noted below). At the closing, we will mail the Warrants and the Depository Trust Company will credit the common stock directly to invest at the address set forth in the securities purchase agreement.

We have agreed to reimburse the purchasers for certain specified expenses, including the fees and disbursements of its legal counsel, in an amount not to exceed \$25,000.

The foregoing descriptions of the securities purchase agreement are only summaries, do not purport to be complete and are qualified in their entirety by reference to the securities purchase agreement, a copy of which is attached as an exhibit to our Current Report on Form 8-K filed with the SEC in connection with this offering and are incorporated herein by reference.

LEGAL MATTERS

Cooley LLP will pass upon the validity of the shares of common stock offered hereby.

EXPERTS

The financial statements incorporated in this Prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus supplement and the accompanying prospectus are part of a registration statement on Form S-3 we filed with the SEC under the Securities Act and does not contain all the information set forth in the registration statement. Whenever a reference is made in this prospectus supplement or the accompanying prospectus to any of our contracts, agreements or other documents, the reference may not be complete and you should refer to the exhibits that are a part of the registration statement or the exhibits to the reports or other documents incorporated by reference therein. For further information with respect to us and the common stock we are offering under this prospectus supplement, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy any document we file with the SEC at the SEC's public reference room at 100 F Street, N.E., Washington, D.C., 20549. Please call the SEC at 1.800.SEC.0330 for further information on the operation of the public reference room. Our SEC filings are also available to the public at the SEC's website at <http://www.sec.gov>.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with it, which means that we can disclose important information to you by referring you to those documents instead of having to repeat the information in this prospectus supplement and the accompanying prospectus. The information incorporated by reference is considered to be part of this prospectus supplement and the accompanying prospectus, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings we will make with the SEC under Sections 13(a), 13(c), 14, or 15(d) of the Exchange Act until the termination of the offering of the shares covered by this prospectus supplement and the accompanying prospectus (other than information furnished under Item 2.02 or Item 7.01 or related exhibits furnished pursuant to Item 9.01 of Form 8-K):

- our annual report on Form 10-K for the year ended December 31, 2017, filed with the SEC on March 7, 2018, including the information specifically incorporated by reference therein from our definitive proxy statement on Schedule 14A, filed on April 18, 2018;
- our quarterly report on Form 10-Q for the quarter ended March 31, 2018, filed with the SEC on May 9, 2018;
- our current reports on Form 8-K, filed with the SEC on February 27, 2018, March 26, 2018, May 16, 2018 and May 31, 2018; and
- the description of our common stock set forth in our registration statement on Form 8-A, filed with the SEC on August 9, 2016, including any amendments thereto or reports filed for the purposes of updating this description.

We will furnish without charge to each person, including any beneficial owner, to whom a prospectus is delivered, upon written or oral request, a copy of any or all of the documents incorporated by reference, including exhibits to these documents. Any such request may be made by writing or telephoning us at the following address or phone number:

Protagonist Therapeutics, Inc.
7707 Gateway Boulevard, Suite 140
Newark, California 94560
(510) 474-0170
Attn: Chief Financial Officer

PROSPECTUS



\$200,000,000

Common Stock

Preferred Stock

Debt Securities

We may, from time to time, offer and sell up to \$200,000,000 of any combination of our common stock, preferred stock or debt securities described in this prospectus, either individually or in combination, at prices and on terms described in one or more supplements to this prospectus. We may also offer common stock or preferred stock upon conversion of debt securities, or common stock upon conversion of preferred stock.

This prospectus describes some of the general terms that may apply to an offering of our securities. We will provide the specific terms of these offerings and securities in one or more supplements to this prospectus. We may also authorize one or more free writing prospectuses to be provided to you in connection with these offerings. The prospectus supplement and any related free writing prospectus may also add, update or change information contained in this prospectus. You should carefully read this prospectus, the applicable prospectus supplement and any related free writing prospectus, as well as the documents incorporated by reference, before buying any of the securities being offered.

This prospectus may not be used to consummate a sale of securities unless accompanied by a prospectus supplement.

Securities may be sold by us to or through underwriters or dealers, directly to purchasers or through agents designated from time to time. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus and in the applicable prospectus supplement. If any underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such underwriters and any applicable discounts or commissions and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds we expect to receive from such sale will also be set forth in a prospectus supplement.

Our common stock is listed on the NASDAQ Global Market under the symbol "PTGX." On August 31, 2017, the last reported sale price of our common stock on the NASDAQ Global Market was \$16.33 per share.

Investing in our securities involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "Risk Factors" contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the other documents that are incorporated by reference into this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is October 5, 2017.

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You should rely only on the information contained in, or incorporated by reference into, this prospectus and the applicable prospectus supplement, along with the information contained in any free writing prospectuses we have authorized for use in connection with a specific offering. We have not authorized anyone to provide you with different information. We are not making an offer to sell or seeking an offer to buy securities under this prospectus or the applicable prospectus supplement and any related free writing prospectus in any jurisdiction where the offer or sale is not permitted. The information contained in this prospectus, the applicable prospectus supplement or any related free writing prospectus, and the documents incorporated by reference herein and therein, are accurate only as of their respective dates, regardless of the time of delivery of this prospectus, the applicable prospectus supplement or any related free writing prospectus, or any sale of a security.

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, using a "shelf" registration process. Under this shelf registration statement, we may sell from time to time in one or more offerings up to a total dollar amount of \$200,000,000 of common stock and preferred stock, and various series of debt securities. Each time we sell any type or series of securities under this prospectus, we will provide a prospectus supplement that will contain more specific information about the terms of that offering. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. We may also add, update or change in a prospectus supplement or free writing prospectus any of the information contained in this prospectus or in the documents we have incorporated by reference into this prospectus. This prospectus, together with the applicable prospectus supplement, any related free writing prospectus and the documents incorporated by reference into this prospectus and the applicable prospectus supplement, will include all material information relating to the applicable offering. You should carefully read both this prospectus and the applicable prospectus supplement and any related free writing prospectus, together with the additional information described under "Where You Can Find More Information," before buying any of the securities being offered.

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This prospectus may not be used to consummate a sale of securities unless accompanied by a prospectus supplement.

This prospectus contains and incorporates by reference market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe that these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. Although we are not aware of any misstatements regarding the market and industry data presented in this prospectus and the documents incorporated herein by reference, these estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under the heading "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the section entitled "Where You Can Find More Information."

Except as otherwise indicated herein or as the context otherwise requires, references in this prospectus to "Protagonist," "the company," "we," "us," "our" and similar references refer to Protagonist Therapeutics, Inc., a corporation under the laws of the State of Delaware.

This prospectus and the information incorporated herein by reference include trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included or incorporated by reference into this prospectus, any applicable prospectus supplement or any related free writing prospectus are the property of their respective owners.

SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference herein and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, the applicable prospectus supplement and any related free writing prospectus, including the risks of investing in our securities discussed under the heading "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our financial statements and related notes, and the exhibits to the registration statement of which this prospectus is a part, before making your investment decision.

Protagonist Therapeutics, Inc.

Overview

We are a clinical-stage biopharmaceutical company with a proprietary technology platform which is utilized to discover and develop novel peptide-based drugs to address significant unmet medical needs. Our primary focus is on developing potential first-in-class oral targeted therapy-based peptide drugs that work by blocking biological pathways that are currently targeted by marketed injectable antibody drugs. Our initial lead peptide product candidates, PTG-100 and PTG-200, are based on this approach, and we believe these candidates have the potential to transform the existing treatment paradigm for inflammatory bowel disease ("IBD"), chronic gastrointestinal diseases consisting primarily of ulcerative colitis ("UC") and Crohn's disease ("CD").

PTG-100, a potential first-in-class oral, alpha-4-beta-7 (" $\alpha4\beta7$ ") integrin antagonist, is currently in a global Phase 2B clinical trial for the treatment of moderate-to-severe UC that is anticipated to randomize approximately 240 patients at approximately 100 clinical sites. We anticipate completing this trial in the second half of 2018. PTG-200, a potential first-in-class oral Interleukin-23 receptor ("IL-23R") antagonist for the potential treatment of CD, is currently in pre-clinical development and is expected to enter Phase 1 clinical studies in the second half of 2017. We have a worldwide collaboration agreement with Janssen Biotech, Inc. to co-develop and commercialize PTG-200 for all indications, including IBD, as described below in the section titled "*Janssen Collaboration Agreement*." In addition to PTG-100 and PTG-200, we are also developing an injectable hepcidin mimetic, PTG-300, for the treatment of rare diseases such as beta-thalassemia. PTG-300 is currently being studied in a Phase 1 clinical trial.

We have not generated any revenue from product sales and we do not currently have any products approved for commercialization. We have never been profitable and have incurred net losses in each year since inception and we do not anticipate that we will achieve profitability in the near term. Our net losses were \$15.0 million and \$29.1 million for the three and six months ended June 30, 2017, respectively, and \$7.1 million and \$18.8 million for the three and six months ended June 30, 2016, respectively. As of June 30, 2017, we had an accumulated deficit of \$93.7 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, development and other expenses related to our ongoing operations and product development, including clinical development activities under the Janssen Collaboration Agreement, and as a result, we expect to continue to incur losses for the foreseeable future. We also expect these losses to increase as we continue our development of, and seek regulatory approval for, our product candidates.

Janssen Collaboration Agreement

On May 26, 2017, we and Janssen Biotech, Inc., ("Janssen") entered into an exclusive license and collaboration agreement (the "Janssen Collaboration Agreement") for the development, manufacture and commercialization of PTG-200 worldwide for the treatment of CD and UC. The Janssen Collaboration Agreement became effective on July 13, 2017. Upon the effectiveness of the agreement, we became eligible for a non-refundable, upfront cash payment of \$50.0 million from Janssen, which we received during the third quarter of 2017.

Under the Janssen Collaboration Agreement, we granted Janssen an exclusive worldwide license to develop, manufacture and commercialize PTG-200 and related IL-23R compounds for all indications, including CD and UC. We are responsible, at our own expense, for the conduct of the Phase 1 clinical trial for PTG-200, and Janssen will be responsible for the conduct of a potential Phase 2 clinical trial for PTG-200 in CD. All such clinical trials would be conducted in accordance with a mutually agreed upon clinical development plan and budget. Development costs for the Phase 2 clinical trial would be shared between the parties on an 80%/20% basis, with Janssen assuming the larger share. Should Janssen elect to retain its license following completion of the Phase 2 clinical trial, it would be responsible, at its own expense, for the manufacture, continued development of, seeking regulatory approval for, and commercialization of PTG-200 worldwide. The parties' development activities under the Janssen Collaboration Agreement through the Phase 2 clinical trial will be overseen by a joint governance structure which will have equal representation by both parties.

Following the conclusion of the planned Phase 2A portion of the Phase 2 clinical trial, if Janssen elects to maintain its license rights and continue the development of PTG-200 in the Phase 2B portion of such clinical trial (the "First Opt-in Election"), we would be eligible to receive a \$125 million payment. Following the conclusion of the planned Phase 2B portion of the Phase 2 clinical trial, if Janssen elects again to maintain its license rights (the "Second Opt-in Election"), we would be eligible to receive a \$200 million payment. In addition to the opt-in fees, we are eligible to receive potential development, regulatory and sales milestone payments of up to an aggregate of \$615 million and tiered royalties paid as a percentage of Janssen's worldwide net sales at rates ranging from ten to the mid-teens, with certain customary reductions in certain circumstances. If Janssen does not make either the First Opt-in Election or the Second Opt-in Election, the Janssen Collaboration Agreement would terminate. If Janssen does not make the Second Opt-in Election, or if at any time after the Second Opt-in Election, Janssen terminates the Janssen Collaboration Agreement, we would be obligated to pay Janssen a royalty on worldwide net sales of PTG-200. We would also have an option to provide up to 30% of the required U.S. details for PTG-200 to prescribers, using our own sales force personnel, upon commercial launch in the United States. If such right is exercised, our detailing costs would be reimbursed by Janssen.

The Janssen Collaboration Agreement contains customary representations, warranties and covenants by us and Janssen and includes an obligation by us not to develop or commercialize other compounds which also target IL-23R outside of the Janssen Collaboration Agreement until completion of the Phase 2B portion of the Phase 2 clinical trial. We and Janssen are required to indemnify the other party against all losses and expenses related to breaches of its representations, warranties and covenants under the Janssen Collaboration Agreement.

The Janssen Collaboration Agreement remains in effect until the royalty obligations cease following patent and regulatory expiry, unless terminated earlier. Either we or Janssen may terminate the Janssen Collaboration Agreement for uncured material breach. Janssen retains the right to terminate the Janssen Collaboration Agreement for convenience and without cause on written notice of a certain period to us. Upon a termination of the Janssen Collaboration Agreement, all rights revert back to us, and in certain circumstances, if such termination occurs during ongoing clinical trials,

Janssen would, if requested, provide certain financial and operational support to us for the completion of such trials.

Company Information

Protagonist Pty Limited (Protagonist Australia) was incorporated in Australia in September 2001. We were incorporated under the laws of the State of Delaware in 2006, under the name Protagonist Therapeutics, Inc., and became the parent of Protagonist Australia pursuant to a transaction in which all of the issued and outstanding capital stock of Protagonist Australia was exchanged for shares of our common stock and Series A preferred stock. Our principal executive offices are located at 7707 Gateway Boulevard, Suite 140, Newark, California 94560. Our telephone number is (510) 474-0170. Our website address is www.protagonist-inc.com. The information contained in, or accessible through, our website does not constitute part of this prospectus, should not be relied on in determining whether to make an investment decision, and the inclusion of our website address in this prospectus is an inactive textual reference only.

The Protagonist logo and other trademarks or service marks of Protagonist Therapeutics, Inc. appearing in this prospectus are the property of Protagonist Therapeutics, Inc. Other trademarks, service marks or trade names appearing in this prospectus are the property of their respective owners. We do not intend our use or display of other companies' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

Risks Associated with our Business

Our business is subject to numerous risks, as described under the heading "Risk Factors" contained in the applicable prospectus supplement and in any free writing prospectuses we have authorized for use in connection with a specific offering, and under similar headings in the documents that are incorporated by reference into this prospectus.

THE SECURITIES WE MAY OFFER

We may offer shares of our common stock and preferred stock, and various series of debt securities, either individually or in combination, with a total dollar amount up to \$200,000,000 from time to time under this prospectus, together with the applicable prospectus supplement and any related free writing prospectus, at prices and on terms to be determined at the time of any offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- maturity;
- original issue discount;
- rates and times of payment of interest or dividends;
- redemption, conversion, exercise, exchange or sinking fund terms;
- ranking;
- restrictive covenants;
- voting or other rights;
- conversion or exchange prices or rates and, if applicable, any provisions for changes to or adjustments in the conversion or exchange prices or rates and in the securities or other property receivable upon conversion or exchange; and
- a discussion of material United States federal income tax considerations, if any.

The applicable prospectus supplement and any related free writing prospectus that we may authorize to be provided to you may also add, update or change information contained in this prospectus or in documents we have incorporated by reference. However, no prospectus supplement or free writing prospectus will offer a security that is not registered and described in this prospectus at the time of the effectiveness of the registration statement of which this prospectus is a part.

This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

We may sell the securities directly to investors or to or through agents, underwriters or dealers. We, and our agents, underwriters or dealers reserve the right to accept or reject all or part of any proposed purchase of securities. If we do offer securities to or through agents, underwriters or dealers, we will include in the applicable prospectus supplement:

- the names of those agents, underwriters or dealers;
- applicable fees, discounts and commissions to be paid to them;
- details regarding over-allotment options, if any; and
- the net proceeds to us.

Common Stock.

We may issue shares of our common stock from time to time. Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the

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election of directors. Under our amended and restated certificate of incorporation, or certificate of incorporation, and amended and restated bylaws, or bylaws, our stockholders do not have cumulative voting rights. Because of this, the holders of a majority of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they should so choose. Subject to preferences that may be applicable to any then-outstanding preferred stock, holders of common stock are entitled to receive ratably those dividends, if any, as may be declared from time to time by our board of directors out of legally available funds. In the event of our liquidation, dissolution or winding up, holders of common stock are entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock. Holders of common stock have no preemptive, conversion or subscription rights and there are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate in the future. In this prospectus, we have summarized certain general features of the common stock under "Description of Capital Stock—Common Stock." We urge you, however, to read the applicable prospectus supplement (and any related free writing prospectus that we may authorize to be provided to you) related to any common stock being offered.

Preferred Stock.

We may issue shares of our preferred stock from time to time, in one or more series. Our board of directors will determine the designations, voting powers, preferences and rights of the preferred stock, as well as the qualifications, limitations or restrictions thereof, including dividend rights, conversion rights, preemptive rights, terms of redemption or repurchase, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of any series. Convertible preferred stock will be convertible into our common stock or exchangeable for other securities. Conversion may be mandatory or at your option and would be at prescribed conversion rates.

If we sell any series of preferred stock under this prospectus, we will fix the designations, voting powers, preferences and rights of such series of preferred stock, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock that we are offering before the issuance of the related series of preferred stock. In this prospectus, we have summarized certain general features of the preferred stock under "Description of Capital Stock—Preferred Stock." We urge you to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the series of preferred stock being offered, as well as the complete certificate of designation that contains the terms of the applicable series of preferred stock.

Debt Securities.

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. The senior debt securities will rank equally with any other unsecured and unsubordinated debt. The subordinated debt securities will be subordinate and junior in right of payment, to the extent and in the manner described in the instrument governing the debt, to all of our senior indebtedness. Convertible debt securities will be convertible into or exchangeable for our common stock or other securities. Conversion may be mandatory or at your option and would be at prescribed conversion rates.

Any debt securities issued under this prospectus will be issued under one or more documents called indentures, which are contracts between us and a national banking association or other eligible

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party, as trustee. In this prospectus, we have summarized certain general features of the debt securities under "Description of Debt Securities." We urge you, however, to read the applicable prospectus supplement (and any free writing prospectus that we may authorize to be provided to you) related to the series of debt securities being offered, as well as the complete indentures that contain the terms of the debt securities. A form of indenture has been filed as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

Use of Proceeds

Except as described in any applicable prospectus supplement or in any free writing prospectus we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from the sale of the shares of our securities offered by us hereunder, if any, for working capital, capital expenditures and other general corporate purposes. See "Use of Proceeds" in this prospectus.

NASDAQ Global Market Listing

Our common stock is listed on the NASDAQ Global Market under the symbol "PTGX." The applicable prospectus supplement will contain information, where applicable, as to other listings, if any, on the NASDAQ Global Market or other securities exchange of the shares of our common stock covered by the applicable prospectus supplement.

RISK FACTORS

Investing in our securities involves a high degree of risk. Before deciding whether to invest in our securities, you should consider carefully the risks and uncertainties described under the heading "Risk Factors" contained in the applicable prospectus supplement and any related free writing prospectus, and discussed under the section entitled "Risk Factors" contained in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering. The risks described in these documents are not the only ones we face, but those that we consider to be material. There may be other unknown or unpredictable economic, business, competitive, regulatory or other factors that could have material adverse effects on our future results. Past financial performance may not be a reliable indicator of future performance, and historical trends should not be used to anticipate results or trends in future periods. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment. Please also read carefully the section below entitled "Forward-Looking Statements."

FORWARD-LOOKING STATEMENTS

This prospectus, including the documents that we incorporate by reference herein, contains, and any applicable prospectus supplement or free writing prospectus including the documents we incorporate by reference therein may contain, forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, and amended, or the Exchange Act, including statements regarding our future financial condition, business strategy and plans and objectives of management for future operations. Forward-looking statements include all statements that are not historical facts. In some cases, you can identify forward-looking statements by terminology such as "believe," "will," "may," "estimate," "continue," "anticipate," "intend," "should," "plan," "might," "approximately," "expect," "predict," "could," "potentially" or the negative of these terms or other similar expressions. Forward-looking statements appear in a number of places throughout this prospectus and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, the potential for our programs, the timing of our clinical trials, the potential for eventual regulatory approval and commercialization of our product candidates and our potential receipt of milestone payments and royalties under our collaboration agreement with Janssen, future operating results or the ability to generate sales, income or cash flow are forward-looking statements.

Discussions containing these forward-looking statements may be found, among other places, in the Sections entitled "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" incorporated by reference from our most recent Annual Report on Form 10-K and in our Quarterly Reports on Form 10-Q, as well as any amendments thereto, filed with the SEC. These statements relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that could cause our actual results, levels of activity, performance or achievement to differ materially from those expressed or implied by these forward-looking statements. We discuss in greater detail, and incorporate by reference into this prospectus in their entirety, many of these risks and uncertainties under the heading "Risk Factors" contained in the applicable prospectus supplement, in any free writing prospectus we may authorize for use in connection with a specific offering, and in our most recent Annual Report on Form 10-K and in our most recent Quarterly Report on Form 10-Q, as well as any amendments thereto reflected in subsequent filings with the SEC. In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information

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available to us as of the date of this prospectus, 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.

FINANCIAL RATIOS

The following table sets forth, for each of the periods presented, our deficiency of earnings to cover fixed charges. Amounts shown are in thousands.

	Year Ended December 31,			Six Months
	2014	2015	2016	Ended June 30, 2017
Ratio of earnings to fixed charges(1)	N/A	N/A	N/A	N/A
Deficiency of earnings available to cover fixed charges	\$ (11,072)	\$ (14,858)	\$ (37,177)	\$ (14,979)

- (1) For the six months ended June 30, 2017 and years ended December 31, 2016, 2015 and 2014, earnings were not sufficient to cover fixed charges. Earnings consist of loss from continuing operations before income taxes, extraordinary items, cumulative effect of accounting changes, equity in net losses of affiliates and fixed charges, adjusted for capitalized interest. Fixed charges consist of interest expensed and capitalized and amortized premiums, discounts and capitalized expenses related to indebtedness. Because of these deficiencies, the ratio information is not applicable for those periods.

USE OF PROCEEDS

Except as described in any applicable prospectus supplement or in any free writing prospectuses we have authorized for use in connection with a specific offering, we currently intend to use the net proceeds from this offering for working capital and general corporate purposes, which may include, among other things, funding research and development, clinical trials, vendor payables, potential regulatory submissions, hiring additional personnel and capital expenditures.

DESCRIPTION OF CAPITAL STOCK

As of the date of this prospectus, our certificate of incorporation, authorizes us to issue up to 90,000,000 shares of common stock, \$0.00001 par value per share, and 10,000,000 shares of preferred stock, \$0.00001 par value per share. As of July 31, 2017, 16,902,761 shares of common stock were outstanding and no shares of preferred stock were outstanding.

The following summary describes the material terms of our capital stock. The description of capital stock is qualified by reference to our certificate of incorporation and our bylaws.

Common Stock

Voting Rights

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

Dividend Rights

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

Liquidation

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

Rights and Preferences

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

Preferred Stock

Our board of directors may, without further action by our stockholders, fix the rights, preferences, privileges and restrictions of up to an aggregate of 10,000,000 shares of preferred stock in one or more series and authorize their issuance. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of such series, any or all of which may be greater than the rights of our common stock. The issuance of our preferred stock could adversely affect the voting power of holders of our common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change of control or other corporate action.

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The following summary of terms of our preferred stock is not complete. You should refer to the provisions of our certificate of incorporation and bylaws and the resolutions containing the terms of each class or series of the preferred stock which have been or will be filed with the SEC at or prior to the time of issuance of such class or series of preferred stock and described in the applicable prospectus supplement. The applicable prospectus supplement may also state that any of the terms set forth herein are inapplicable to such series of preferred stock, provided that the information set forth in such prospectus supplement does not constitute material changes to the information herein such that it alters the nature of the offering or the securities offered.

We will fix the designations, voting powers, preferences and rights of the preferred stock of each series we issue under this prospectus, as well as the qualifications, limitations or restrictions thereof, in the certificate of designation relating to that series. We will file as an exhibit to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, the form of any certificate of designation that describes the terms of the series of preferred stock we are offering. We will describe in the applicable prospectus supplement the terms of the series of preferred stock being offered, including, to the extent applicable:

- the title and stated value;
- the number of shares we are offering;
- the liquidation preference per share;
- the purchase price;
- the dividend rate, period and payment date and method of calculation for dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- the procedures for any auction and remarketing;
- the provisions for a sinking fund;
- the provisions for redemption or repurchase, if applicable, and any restrictions on our ability to exercise those redemption and repurchase rights;
- any listing of the preferred stock on any securities exchange or market;
- whether the preferred stock will be convertible into our common stock, and, if applicable, the conversion price, or how it will be calculated, and the conversion period;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange price, or how it will be calculated, and the exchange period;
- voting rights of the preferred stock;
- preemptive rights;
- restrictions on transfer, sale or other assignment;
- whether interests in the preferred stock will be represented by depositary shares;
- a discussion of material United States federal income tax considerations applicable to the preferred stock;
- the relative ranking and preferences of the preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs;

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- any limitations on the issuance of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the preferred stock.

If we issue shares of preferred stock under this prospectus, the shares will be fully paid and non-assessable.

The issuance of preferred stock could adversely affect the voting power of holders of common stock and reduce the likelihood that common stockholders will receive dividend payments and payments upon liquidation. The issuance could have the effect of decreasing the market price of the common stock. The issuance of preferred stock also could have the effect of delaying, deterring or preventing a change in control of us.

Options

As of July 31, 2017, (i) options to purchase an aggregate of 2,509,759 shares of common stock were outstanding and (ii) an additional 562,490 shares were reserved for future issuance under our 2016 Equity Incentive Plan.

Stockholder Registration Rights

Registration Rights

We are party to an amended and restated investors rights agreement that provides that holders of our capital stock, including certain holders of 5% of our capital stock and entities affiliated with certain of our directors, have certain registration rights, as set forth below. The registration of shares of our common stock pursuant to the exercise of registration rights described below would enable the holders to sell these shares without restriction under the Securities Act when the applicable registration statement is declared effective. These shares are referred to as registrable securities. We will pay the registration expenses, other than the underwriting discounts and commissions, of the shares registered pursuant to the demand, piggyback and Form S-3 registrations described below.

Generally, in an underwritten offering, the managing underwriter, if any, has the right, subject to specified conditions, to limit the number of shares such holders may include. The demand, piggyback and Form S-3 registration rights described below will expire upon the earlier of August 10, 2019, or when all investors, considered with their affiliates, can sell all of their shares in a 90-day period under Rule 144.

Demand registration rights

The holders of certain shares of our registerable securities are entitled to certain demand registration rights. The holders of a majority of these shares may, on not more than two occasions, request that we register all or a portion of their shares, subject to certain specified exceptions.

Piggyback registration rights

In connection with this offering, the holders of certain shares of our registrable securities, were entitled to, and the necessary percentage of holders waived, their rights to notice of this offering and to include their shares of registrable securities in this offering. In the event that we propose to register any of our securities under the Securities Act in another offering, either for our own account or for the account of other security holders, the holders of these shares will be entitled to certain "piggyback" registration rights allowing them to include their shares in such registration, subject to certain

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marketing and other limitations. As a result, whenever we propose to file a registration statement under the Securities Act, including a registration statement on Form S-3 as discussed below, other than with respect to a demand registration or a registration statement on Forms S-4 or S-8 or related to stock issued upon conversion of debt securities, the holders of these shares are entitled to notice of the registration and have the right, subject to limitations that the underwriters may impose on the number of shares included in the registration, to include their shares in the registration. However, in no event shall the aggregate value of securities of the selling stockholders included in the offering be reduced below twenty-five percent of the total value of all of securities included in such offering.

Form S-3 registration rights

The holders of certain shares of our registrable securities are entitled to certain Form S-3 registration rights, provided that we have not already effected two such registrations within the twelve-month period preceding the date of such request. Such holders may make a request that we register their shares on Form S-3 if we are qualified to file a registration statement on Form S-3. Such request for registration on Form S-3 must cover securities the aggregate offering price of which, before payment of underwriting discounts and commissions, is at least \$2.5 million.

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

Some provisions of Delaware law, our certificate of incorporation and our bylaws contain provisions that could make the following transactions more difficult: an acquisition of us by means of a tender offer; an acquisition of us by means of a proxy contest or otherwise; or the removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult to accomplish or could deter transactions that stockholders may otherwise consider to be in their best interest or in our best interests, including transactions which provide for payment of a premium over the market price for our shares.

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

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

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

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

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

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

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

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

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

Choice of Forum—Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of a fiduciary duty or other wrongdoing by any of our directors, officers, employees or agents to us or our stockholders; (3) any action asserting a claim against us arising pursuant to any provision of the General Corporation Law of the State of Delaware or our certificate of incorporation or bylaws; (4) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws; or (5) any action asserting a claim governed by the internal affairs doctrine. Our certificate of incorporation also provides that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock will be deemed to have notice of and to have consented to this choice of forum provision. It is possible that a court of law could rule that the choice of forum provision contained in our certificate of incorporation is inapplicable or unenforceable if it is challenged in a proceeding or otherwise.

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

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

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Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent's address is 6201 15th Avenue, Brooklyn, New York 11219. The transfer agent for any series of preferred stock that we may offer under this prospectus will be named and described in the prospectus supplement for that series.

Listing on the NASDAQ Global Market

Our common stock is listed on the NASDAQ Global Market under the symbol "PTGX." The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on the NASDAQ Capital Market or any securities market or other exchange of the preferred stock covered by such prospectus supplement.

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any debt securities that we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below. Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue the debt securities under the indenture that we will enter into with the trustee named in the indenture. The indenture will be qualified under the Trust Indenture Act of 1939, as amended, or the Trust Indenture Act. We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part or will be incorporated by reference from reports that we file with the SEC.

The following summary of material provisions of the debt securities and the indenture is subject to, and qualified in its entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectus related to the debt securities that we may offer under this prospectus, as well as the complete indenture that contains the terms of the debt securities.

General

The indenture does not limit the amount of debt securities that we may issue. It provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit that we may designate. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to give holders of any debt securities protection against changes in our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as "discount securities," which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may be issued with "original issue discount," or OID, for U.S. federal income tax purposes because of interest payment and other characteristics or terms of the debt securities. Material U.S. federal income tax considerations applicable to debt securities issued with OID will be described in more detail in any applicable prospectus supplement.

We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

- the title of the series of debt securities;
- any limit upon the aggregate principal amount that may be issued;
- the maturity date or dates;
- the form of the debt securities of the series;
- the applicability of any guarantees;
- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;

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- whether the debt securities rank as senior debt, senior subordinated debt, subordinated debt or any combination thereof, and the terms of any subordination;
- if the price (expressed as a percentage of the aggregate principal amount thereof) at which such debt securities will be issued is a price other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof, or if applicable, the portion of the principal amount of such debt securities that is convertible into another security or the method by which any such portion shall be determined;
- the interest rate or rates, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;
- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- if applicable, the date or dates after which, or the period or periods during which, and the price or prices at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;
- the date or dates, if any, on which, and the price or prices at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;
- the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof;
- any and all terms, if applicable, relating to any auction or remarketing of the debt securities of that series and any security for our obligations with respect to such debt securities and any other terms which may be advisable in connection with the marketing of debt securities of that series;
- whether the debt securities of the series shall be issued in whole or in part in the form of a global security or securities; the terms and conditions, if any, upon which such global security or securities may be exchanged in whole or in part for other individual securities; and the depository for such global security or securities;
- if applicable, the provisions relating to conversion or exchange of any debt securities of the series and the terms and conditions upon which such debt securities will be so convertible or exchangeable, including the conversion or exchange price, as applicable, or how it will be calculated and may be adjusted, any mandatory or optional (at our option or the holders' option) conversion or exchange features, the applicable conversion or exchange period and the manner of settlement for any conversion or exchange;
- if other than the full principal amount thereof, the portion of the principal amount of debt securities of the series which shall be payable upon declaration of acceleration of the maturity thereof;
- additions to or changes in the covenants applicable to the particular debt securities being issued, including, among others, the consolidation, merger or sale covenant;
- additions to or changes in the events of default with respect to the securities and any change in the right of the trustee or the holders to declare the principal, premium, if any, and interest, if any, with respect to such securities to be due and payable;
- additions to or changes in or deletions of the provisions relating to covenant defeasance and legal defeasance;

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- additions to or changes in the provisions relating to satisfaction and discharge of the indenture;
- additions to or changes in the provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;
- the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars;
- whether interest will be payable in cash or additional debt securities at our or the holders' option and the terms and conditions upon which the election may be made;
- the terms and conditions, if any, upon which we will pay amounts in addition to the stated interest, premium, if any and principal amounts of the debt securities of the series to any holder that is not a "United States person" for federal tax purposes;
- any restrictions on transfer, sale or assignment of the debt securities of the series; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, any other additions or changes in the provisions of the indenture, and any terms that may be required by us or advisable under applicable laws or regulations.

Conversion or Exchange Rights

We will set forth in the prospectus supplement the terms on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indenture will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of our assets as an entirety or substantially as an entirety. However, any successor to or acquirer of such assets (other than a subsidiary of ours) must assume all of our obligations under the indenture or the debt securities, as appropriate.

Events of Default under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indenture with respect to any series of debt securities that we may issue:

- if we fail to pay any installment of interest on any series of debt securities, as and when the same shall become due and payable, and such default continues for a period of 90 days; provided, however, that a valid extension of an interest payment period by us in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of interest for this purpose;
- if we fail to pay the principal of, or premium, if any, on any series of debt securities as and when the same shall become due and payable whether at maturity, upon redemption, by declaration or otherwise, or in any payment required by any sinking or analogous fund established with respect to such series; provided, however, that a valid extension of the maturity of such debt securities in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of principal or premium, if any;

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- if we fail to observe or perform any other covenant or agreement contained in the debt securities or the indenture, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive written notice of such failure, requiring the same to be remedied and stating that such is a notice of default thereunder, from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal of, premium, if any, and accrued interest, if any, due and payable immediately. If an event of default specified in the last bullet point above occurs with respect to us, the principal amount of and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indenture, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies only if:

- the holder has given written notice to the trustee of a continuing event of default with respect to that series;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request;
- such holders have offered to the trustee indemnity satisfactory to it against the costs, expenses and liabilities to be incurred by the trustee in compliance with the request; and
- the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

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These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indenture.

Modification of Indenture; Waiver

We and the trustee may change an indenture without the consent of any holders with respect to specific matters:

- to cure any ambiguity, defect or inconsistency in the indenture or in the debt securities of any series;
- to comply with the provisions described above under "Description of Debt Securities—Consolidation, Merger or Sale;"
- to provide for uncertificated debt securities in addition to or in place of certificated debt securities;
- to add to our covenants, restrictions, conditions or provisions such new covenants, restrictions, conditions or provisions for the benefit of the holders of all or any series of debt securities, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred upon us in the indenture;
- to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;
- to make any change that does not adversely affect the interests of any holder of debt securities of any series in any material respect;
- to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided above under "Description of Debt Securities—General" to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;
- to evidence and provide for the acceptance of appointment under any indenture by a successor trustee; or
- to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act.

In addition, under the indenture, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of any debt securities of any series;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption of any series of any debt securities; or

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- reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

- provide for payment;
- register the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- pay principal of and premium and interest on any debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- recover excess money held by the trustee;
- compensate and indemnify the trustee; and
- appoint any successor trustee.

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company, or DTC, or another depository named by us and identified in a prospectus supplement with respect to that series. To the extent the debt securities of a series are issued in global form and as book-entry, a description of terms relating such securities will be set forth in the applicable prospectus supplement.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a

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change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indenture at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the internal laws of the State of New York, except to the extent that the Trust Indenture Act of 1939 is applicable.

LEGAL OWNERSHIP OF SECURITIES

We can issue securities in registered form or in the form of one or more global securities. We describe global securities in greater detail below. We refer to those persons who have securities registered in their own names on the books that we or any applicable trustee, depositary or warrant agent maintain for this purpose as the "holders" of those securities. These persons are the legal holders of the securities. We refer to those persons who, indirectly through others, own beneficial interests in securities that are not registered in their own names, as "indirect holders" of those securities. As we discuss below, indirect holders are not legal holders, and investors in securities issued in book-entry form or in street name will be indirect holders.

Book-Entry Holders

We may issue securities in book-entry form only, as we will specify in the applicable prospectus supplement. This means securities may be represented by one or more global securities registered in the name of a financial institution that holds them as depositary on behalf of other financial institutions that participate in the depositary's book-entry system. These participating institutions, which are referred to as participants, in turn, hold beneficial interests in the securities on behalf of themselves or their customers.

Only the person in whose name a security is registered is recognized as the holder of that security. Securities issued in global form will be registered in the name of the depositary or its participants. Consequently, for securities issued in global form, we will recognize only the depositary as the holder of the securities, and we will make all payments on the securities to the depositary. The depositary passes along the payments it receives to its participants, which in turn pass the payments along to their customers who are the beneficial owners. The depositary and its participants do so under agreements they have made with one another or with their customers; they are not obligated to do so under the terms of the securities.

As a result, investors in a global security will not own securities directly. Instead, they will own beneficial interests in a global security, through a bank, broker or other financial institution that participates in the depositary's book-entry system or holds an interest through a participant. As long as the securities are issued in global form, investors will be indirect holders, and not legal holders, of the securities.

Street Name Holders

We may terminate a global security or issue securities in non-global form. In these cases, investors may choose to hold their securities in their own names or in "street name." Securities held by an investor in street name would be registered in the name of a bank, broker or other financial institution that the investor chooses, and the investor would hold only a beneficial interest in those securities through an account he or she maintains at that institution.

For securities held in street name, we or any applicable trustee or depositary will recognize only the intermediary banks, brokers and other financial institutions in whose names the securities are registered as the holders of those securities, and we or any applicable trustee or depositary will make all payments on those securities to them. These institutions pass along the payments they receive to their customers who are the beneficial owners, but only because they agree to do so in their customer agreements or because they are legally required to do so. Investors who hold securities in street name will be indirect holders, not holders, of those securities.

Legal Holders

Our obligations, as well as the obligations of any applicable trustee and of any third parties employed by us or a trustee, run only to the legal holders of the securities. We do not have obligations to investors who hold beneficial interests in global securities, in street name or by any other indirect means. This will be the case whether an investor chooses to be an indirect holder of a security or has no choice because we are issuing the securities only in global form.

For example, once we make a payment or give a notice to the legal holder, we have no further responsibility for the payment or notice even if that legal holder is required, under agreements with its participants or customers or by law, to pass it along to the indirect holders but does not do so. Similarly, we may want to obtain the approval of the legal holders to amend an indenture, to relieve us of the consequences of a default or of our obligation to comply with a particular provision of the indenture or for other purposes. In such an event, we would seek approval only from the holders, and not the indirect holders, of the securities. Whether and how the legal holders contact the indirect holders is up to the legal holders.

Special Considerations for Indirect Holders

If you hold securities through a bank, broker or other financial institution, either in book-entry form because the securities are represented by one or more global securities or in street name, you should check with your own institution to find out:

- how it handles securities payments and notices;
- whether it imposes fees or charges;
- how it would handle a request for the holders' consent, if ever required;
- whether and how you can instruct it to send you securities registered in your own name so you can be a holder, if that is permitted in the future;
- how it would exercise rights under the securities if there were a default or other event triggering the need for holders to act to protect their interests; and
- if the securities are in book-entry form, how the depositary's rules and procedures will affect these matters.

Global Securities

A global security is a security that represents one or any other number of individual securities held by a depositary. Generally, all securities represented by the same global securities will have the same terms.

Each security issued in book-entry form will be represented by a global security that we issue to, deposit with and register in the name of a financial institution or its nominee that we select. The financial institution that we select for this purpose is called the depositary. Unless we specify otherwise in the applicable prospectus supplement, DTC will be the depositary for all securities issued in book-entry form.

A global security may not be transferred to or registered in the name of anyone other than the depositary, its nominee or a successor depositary, unless special termination situations arise. We describe those situations below under "Special Situations When a Global Security Will Be Terminated." As a result of these arrangements, the depositary, or its nominee, will be the sole registered owner and legal holder of all securities represented by a global security, and investors will be permitted to own only beneficial interests in a global security. Beneficial interests must be held by means of an account with a broker, bank or other financial institution that in turn has an account with the depositary or with

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another institution that does. Thus, an investor whose security is represented by a global security will not be a legal holder of the security, but only an indirect holder of a beneficial interest in the global security.

If the prospectus supplement for a particular security indicates that the security will be issued in global form only, then the security will be represented by a global security at all times unless and until the global security is terminated. If termination occurs, we may issue the securities through another book-entry clearing system or decide that the securities may no longer be held through any book-entry clearing system.

Special Considerations for Global Securities

The rights of an indirect holder relating to a global security will be governed by the account rules of the investor's financial institution and of the depository, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depository that holds the global security.

If securities are issued only in the form of a global security, an investor should be aware of the following:

- an investor cannot cause the securities to be registered in his or her name, and cannot obtain non-global certificates for his or her interest in the securities, except in the special situations we describe below;
- an investor will be an indirect holder and must look to his or her own bank, broker or other financial institution for payments on the securities and protection of his or her legal rights relating to the securities, as we describe above;
- an investor may not be able to sell interests in the securities to some insurance companies and to other institutions that are required by law to own their securities in non-book-entry form;
- an investor may not be able to pledge his or her interest in a global security in circumstances where certificates representing the securities must be delivered to the lender or other beneficiary of the pledge in order for the pledge to be effective;
- the depository's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in a global security;
- we and any applicable trustee have no responsibility for any aspect of the depository's actions or for its records of ownership interests in a global security, nor do we or any applicable trustee supervise the depository in any way;
- the depository may, and we understand that DTC will, require that those who purchase and sell interests in a global security within its book-entry system use immediately available funds, and your bank, broker or other financial institution may require you to do so as well; and
- financial institutions that participate in the depository's book-entry system, and through which an investor holds its interest in a global security, may also have their own policies affecting payments, notices and other matters relating to the securities.

There may be more than one financial intermediary in the chain of ownership for an investor. We do not monitor and are not responsible for the actions of any of those intermediaries.

Special Situations When a Global Security Will Be Terminated

In a few special situations described below, the global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of

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whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks, brokers or other financial institutions to find out how to have their interests in securities transferred to their own name, so that they will be direct holders. We have described the rights of holders and street name investors above.

Unless we provide otherwise in the applicable prospectus supplement, the global security will terminate when the following special situations occur:

- if the depositary notifies us that it is unwilling, unable or no longer qualified to continue as depositary for that global security and we do not appoint another institution to act as depositary within 90 days;
- if we notify any applicable trustee that we wish to terminate that global security; or
- if an event of default has occurred with regard to securities represented by that global security and has not been cured or waived.

The prospectus supplement may also list additional situations for terminating a global security that would apply only to the particular series of securities covered by the applicable prospectus supplement. When a global security terminates, the depositary, and not we or any applicable trustee, is responsible for deciding the names of the institutions that will be the initial direct holders.

PLAN OF DISTRIBUTION

We may sell our securities covered by this prospectus in any of three ways (or in any combination):

- to or through underwriters or dealers;
- directly to one or more purchasers; or
- through agents.

We may distribute the securities:

- from time to time in one or more transactions at a fixed price or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to the prevailing market prices; or
- at negotiated prices.

Each time we offer and sell securities covered by this prospectus, we will provide a prospectus supplement or supplements that will describe the method of distribution and set forth the terms of the offering, including:

- the name or names of any underwriters, dealers or agents;
- the amounts of securities underwritten or purchased by each of them;
- the purchase price of securities and the proceeds we will receive from the sale;
- any over-allotment options under which underwriters may purchase additional securities from us;
- any underwriting discounts or commissions or agency fees and other items constituting underwriters' or agents' compensation;
- the public offering price of the securities;
- any discounts, commissions or concessions allowed or reallocated or paid to dealers; and
- any securities exchange or market on which the securities may be listed.

Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may be changed from time to time. We may determine the price or other terms of the securities offered under this prospectus by use of an electronic auction. We will describe how any auction will determine the price or any other terms, how potential investors may participate in the auction and the nature of the obligations of the underwriter, dealer or agent in the applicable prospectus supplement.

Underwriters or dealers may offer and sell the offered securities from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. If underwriters or dealers are used in the sale of any securities, the securities will be acquired by the underwriters or dealers for their own account and may be resold from time to time in one or more transactions described above. The securities may be either offered to the public through underwriting syndicates represented by managing underwriters, or directly by underwriters or dealers. Generally, the underwriters' or dealers' obligations to purchase the securities will be subject to certain conditions precedent. The underwriters or dealers will be obligated to purchase all of the securities if they purchase any of the securities, unless otherwise specified in the prospectus supplement. We may use underwriters with whom we have a material relationship. We will describe the nature of any such relationship in the prospectus supplement, naming the underwriter.

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We may sell the securities through agents from time to time. The prospectus supplement will name any agent involved in the offer or sale of the securities and any commissions we pay to them. Generally, any agent will be acting on a best efforts basis for the period of its appointment. We may authorize underwriters, dealers or agents to solicit offers by certain purchasers to purchase the securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified date in the future. The contracts will be subject only to those conditions set forth in the prospectus supplement, and the prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

Agents, dealers and underwriters may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments which the agents, dealers or underwriters may be required to make in respect thereof. Agents, dealers and underwriters may be customers of, engage in transactions with, or perform services for us in the ordinary course of business.

All securities we may offer, other than common stock, will be new issues of securities with no established trading market. Any underwriters may make a market in these securities, but will not be obligated to do so and may discontinue any market making at any time without notice. We cannot guarantee the liquidity of the trading markets for any securities.

Any underwriter may engage in overallotment, stabilizing transactions, short covering transactions and penalty bids in accordance with Regulation M under the Securities Exchange Act of 1934, as amended. Overallotment involves sales in excess of the offering size, which create a short position. This short sales position may involve either "covered" short sales or "naked" short sales. Covered short sales are short sales made in an amount not greater than the underwriters' over-allotment option to purchase additional securities in this offering described above. The underwriters may close out any covered short position either by exercising their over-allotment option or by purchasing securities in the open market. To determine how they will close the covered short position, the underwriters will consider, among other things, the price of securities available for purchase in the open market, as compared to the price at which they may purchase securities through the over-allotment option. Naked short sales are short sales in excess of the over-allotment option. The underwriters must close out any naked short position by purchasing securities in the open market. A naked short position is more likely to be created if the underwriters are concerned that, in the open market after pricing, there may be downward pressure on the price of the securities that could adversely affect investors who purchase securities in this offering. Stabilizing transactions permit bids to purchase the underlying security for the purpose of fixing the price of the security so long as the stabilizing bids do not exceed a specified maximum. Penalty bids permit the underwriters to reclaim a selling concession from a dealer when the securities originally sold by the dealer are purchased in a covering transaction to cover short positions.

Any underwriters who are qualified market makers on the NASDAQ Global Market may engage in passive market making transactions in our common stock, preferred stock and debt securities, as applicable, on the NASDAQ Global Market in accordance with Rule 103 of Regulation M, during the business day prior to the pricing of the offering, before the commencement of offers or sales of the securities. Passive market makers must comply with applicable volume and price limitations and must be identified as passive market makers. In general, a passive market maker must display its bid at a price not in excess of the highest independent bid for such security; if all independent bids are lowered below the passive market maker's bid, however, the passive market maker's bid must then be lowered when certain purchase limits are exceeded.

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Similar to other purchase transactions, an underwriter's purchase to cover the syndicate short sales or to stabilize the market price of our securities may have the effect of raising or maintaining the market price of our securities or preventing or mitigating a decline in the market price of our securities. As a result, the price of our securities may be higher than the price that might otherwise exist in the open market. The imposition of a penalty bid might also have an effect on the price of the securities if it discourages resales of the securities.

Neither we nor the underwriters make any representation or prediction as to the effect that the transactions described above may have on the price of the securities. If such transactions are commenced, they may be discontinued without notice at any time.

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, the validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon for us by Cooley LLP.

EXPERTS

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2016 have been so incorporated in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of a registration statement we filed with the SEC. This prospectus does not contain all of the information set forth in the registration statement and the exhibits to the registration statement. For further information with respect to us and the securities we are offering under this prospectus, we refer you to the registration statement and the exhibits and schedules filed as a part of the registration statement. Neither we nor any agent, underwriter or dealer has authorized any person to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus is accurate as of any date other than the date on the front page of this prospectus, regardless of the time of delivery of this prospectus or any sale of the securities offered by this prospectus.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy any document we file with the SEC at the SEC's public reference room at 100 F Street, N.E., Washington, D.C., 20549. Please call the SEC at 1.800.SEC.0330 for further information on the operation of the public reference room. Our SEC filings are also available to the public at the SEC's website at <http://www.sec.gov>.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with it, which means that we can disclose important information to you by referring you to those documents instead of having to repeat the information in this prospectus. The information incorporated by reference is considered to be part of this prospectus, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference the documents listed below and any future filings (including those made after the date of the initial filing of the registration statement of which this prospectus is a part and prior to the effectiveness of such registration statement) we will make with the SEC under Sections 13(a), 13(c), 14, or 15(d) of the Exchange Act until the termination of the offering of the shares covered by this prospectus (other than information furnished under Item 2.02 or Item 7.01 of Form 8-K):

- our annual report on Form 10-K for the year ended December 31, 2016, filed with the SEC on March 7, 2017, including the information specifically incorporated by reference therein from our definitive proxy statement on Schedule 14A, filed on April 24, 2017;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, filed with the SEC on May 10, 2017;
- our Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, filed with the SEC on August 8, 2017;
- our current reports on Form 8-K, filed with the SEC on February 9, 2017, May 23, 2017, May 25, 2017, May 30, 2017 and June 8, 2017;
- our current report on Form 8-K/A, filed with the SEC on July 31, 2017; and
- the description of our common stock set forth in our registration statement on Form 8-A, filed with the SEC on August 9, 2016, including any amendments thereto or reports filed for the purposes of updating this description.

You can request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Protagonist Therapeutics, Inc.
7707 Gateway Boulevard, Suite 140
Newark, California 94560
(510) 474-0170
Attn: Chief Financial Officer

This prospectus is part of a registration statement we filed with the SEC. That registration statement and the exhibits filed along with the registration statement contain more information about us and the shares in this offering. Because information about documents referred to in this prospectus is not always complete, you should read the full documents which are filed as exhibits to the registration statement. You may read and copy the full registration statement and its exhibits at the SEC's public reference rooms or its website.

2,750,000 Shares



Common Stock

PROSPECTUS SUPPLEMENT

August 7, 2018
