

**PROSPECTUS SUPPLEMENT
(To Prospectus Dated October 17, 2019)****\$17,500,000****Common Stock**

We have entered into an Controlled Equity OfferingSM Sales Agreement (the “sales agreement”) with Cantor Fitzgerald & Co. (“Cantor”), dated as of August 27, 2021, relating to the offer and sale of shares of our common stock. In accordance with the terms of the sales agreement, under this prospectus supplement and the accompanying prospectus, we may offer and sell shares of our common stock having an aggregate offering price of up to \$17,500,000 from time to time through Cantor acting as sales agent.

Our common stock is listed on The Nasdaq Global Market (“Nasdaq”) under the symbol “ETTX.” On August 26, 2021, the last reported sale price of our common stock on Nasdaq was \$2.69 per share. You are urged to obtain current market quotations for our common stock.

Sales of our common stock, if any, under this prospectus supplement and the accompanying prospectus may be made in sales deemed to be “at the market offerings” as defined in Rule 415(a)(4) under the Securities Act of 1933, as amended (the “Securities Act”). This includes sales made directly on Nasdaq or sales made to or through a market maker other than on an exchange. With our prior written consent, sales may also be made in negotiated transactions at market prices prevailing at the time of sale or at prices related to such prevailing market prices or any other method permitted by law. If we and Cantor agree on a method of distribution other than sales of shares of our common stock on or through Nasdaq or another existing U.S. trading market at market prices, we will file a further prospectus supplement providing all information about such offering as required by Rule 424(b) under the Securities Act. Cantor is not required to sell any specific number or dollar amount of securities, but will act as a sales agent using commercially reasonable efforts consistent with its normal trading and sales practices, to sell on our behalf shares of our common stock as designated by us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

Cantor will be entitled to compensation at a fixed commission rate equal to 3.0% of the gross sales price per share sold under the sales agreement. In connection with the sale of the common stock on our behalf, Cantor will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation Cantor receives will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification to and reimburse certain expenses of Cantor in connection with the sales agreement as further described in the Plan of Distribution section beginning on page S-10 of this prospectus supplement.

As of August 16, 2021, the aggregate market value of our outstanding common stock held by non-affiliates was approximately \$53,116,467, which we calculated based on 47,310,254 shares of outstanding common stock that were issued and outstanding as of August 16, 2021, of which 18,637,357 shares were held by non-affiliates, and a price per share of \$2.85 on June 28, 2021. Pursuant to General Instruction I.B.6 of Form S-3, in no event will we sell, pursuant to the registration statement of which this prospectus supplement forms a part, securities in a public primary offering with a value exceeding one-third of the aggregate market value of our outstanding common stock held by non-affiliates in any 12-month period, so long as the aggregate market value of our outstanding common stock held by non-affiliates remains below \$75 million. During the 12 calendar months prior to and including the date of this prospectus supplement, we have not offered or sold any securities pursuant to General Instruction I.B.6 of Form S-3.

Investing in our securities involves a high degree of risk. You should carefully consider the risks described under “Risk Factors” on page S-6 of this prospectus supplement and in the documents incorporated by reference into this prospectus supplement.

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

The logo for Cantor consists of the word "CANTOR" in a bold, blue, sans-serif font. The letters are slightly shadowed, giving it a three-dimensional appearance. The logo is centered between two horizontal lines.

The date of this prospectus supplement is August 27, 2021.

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein and therein. The second part, the accompanying prospectus, provides more general information, some of which does not apply to this offering. If information included or incorporated by reference in this prospectus supplement is inconsistent with the accompanying prospectus or the information incorporated by reference therein, then this prospectus supplement or the information incorporated by reference in this prospectus supplement will apply and will supersede the information in the accompanying prospectus and the documents incorporated by reference therein. For a more detailed understanding of our common stock, you should read both this prospectus supplement and the accompanying prospectus, together with additional information described under the heading “Where You Can Find More Information.”

This prospectus supplement and the accompanying prospectus are part of a registration statement on Form S-3 (File No. 333-234041) that we filed with the SEC on October 2, 2019 and which became effective on October 17, 2019. Under this prospectus supplement, we may offer shares of our common stock having an aggregate offering price of up to \$17,500,000 from time to time at prices and on terms to be determined by market conditions at the time of offering.

Neither we nor Cantor have authorized anyone to provide you with different or additional information from that contained in this prospectus supplement, the accompanying prospectus or any free writing prospectus prepared by us or on our behalf. Neither we nor Cantor take responsibility for, and can provide no assurance as to the reliability of, any information that others may give. Neither we nor Cantor are making an offer to sell or soliciting an offer to buy our common stock under any circumstance in any jurisdiction where the offer or solicitation is not permitted. You should assume that the information contained in this prospectus supplement, the accompanying prospectus or any free writing prospectus prepared by us or on our behalf is accurate only as of the date of the respective document in which the information appears, and that any information in documents that we have incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus supplement, the accompanying prospectus or any sale of a security. Our business, financial condition, results of operations and prospects may have changed since those dates.

We are offering to sell, and seeking offers to buy, shares of common stock only in jurisdictions where offers and sales are permitted. 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 accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

We 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 effective 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.

Unless the context indicates otherwise, references in this prospectus to “Entasis,” “the Company,” “we,” “us,” “our” and similar references refer to Entasis Therapeutics Holdings Inc. and its wholly owned subsidiaries.

FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated herein and therein by reference contain forward-looking statements within the meaning of Section 27A of the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended (the “Exchange Act”). All statements other than statements of historical fact are “forward-looking statements” for purposes of this prospectus supplement, the accompanying prospectus and the documents incorporated herein and therein by reference. In some cases, you can identify forward-looking statements by terminology such as “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would” or the negative or plural of those terms, and similar expressions. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other “forward-looking” information.

Forward-looking statements include, but are not limited to, statements about:

- the severity and duration of the impact of the COVID-19 pandemic on our business, development programs and access to capital;
- our plans to develop and commercialize our product candidates;
- the timing of execution of planned clinical trials and availability of data from our clinical trials;
- our expectation that the efficacy and safety data from our ongoing and planned Phase 3 registrational trials, if positive, will be sufficient to support submission of a new drug application (“NDA”) to the U.S. Food and Drug Administration (the “FDA”);
- our ability to obtain grants or other government funding to develop our product candidates;
- our ability to take advantage of benefits offered by current and pending legislation related to the development of products addressing antimicrobial resistance;
- the timing of and our ability to file, obtain and maintain regulatory filings for our product candidates;
- the clinical utility of our product candidates and their potential advantages compared to other treatments;
- our commercialization, marketing and distribution capabilities and strategy;
- our ability to establish and maintain arrangements for the manufacture of our product candidates;
- our ability to establish and maintain collaborations and to recognize the potential benefits of such collaborations;
- our estimates regarding the market opportunities for our product candidates;
- our intellectual property position and the duration of our patent rights;
- our estimates regarding anticipated operating losses, needs for additional funds and capital requirements;
- political, social and economic instability, natural disasters or public health epidemics in countries where we or our collaborators do business;
- the substantial influence and control that Innoviva, Inc. (“Innoviva”) may exert on actions requiring stockholder approval; and
- our estimated needs for, and ability to raise additional financing, and our ability to continue as a going concern.

The foregoing factors should not be construed as exhaustive and should be read together with the other cautionary statements included in our [Annual Report on Form 10-K, for the year ended December 31,](#)

2020, as updated by our Quarterly Reports on Form 10-Q for the quarters ended [March 31, 2021](#) and [June 30, 2021](#), respectively, particularly in the “Risk Factors” sections of such reports (as updated by the disclosures in our subsequent filings with the SEC that are incorporated by reference herein), that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. Any forward-looking statement in this prospectus supplement, the accompanying prospectus and the documents incorporated herein and therein by reference reflects our current view with respect to future events and is subject to these and other risks, uncertainties and assumptions relating to our operations, results of operations, industry and future growth. Given these uncertainties, you should not rely on these forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Forward-looking statements in this prospectus supplement are made only as of the date hereof and, except as required by law, we assume no obligation to update or revise any forward-looking statements contained in this prospectus supplement, the accompanying prospectus or any information incorporated by reference herein or therein, whether as a result of any new information, future events or otherwise.

PROSPECTUS SUPPLEMENT SUMMARY

The following summary highlights information contained elsewhere in this prospectus supplement. This summary is not complete and does not contain all of the information that you need to consider before making an investment decision. For a more complete understanding of our Company, you should read and consider carefully the more detailed information included or incorporated by reference in this prospectus supplement, including the factors described under the heading “Risk Factors” beginning on page S-5 of this prospectus supplement, as well as the information incorporated by reference from our most recent Annual Report on Form 10-K and our most recent Quarterly Report on Form 10-Q, before making an investment decision.

Company Overview

We are an advanced, clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of novel antibacterial products that address high unmet need to treat serious infections caused by multidrug-resistant Gram-negative bacteria.

Our lead product candidate, sulbactam-durlobactam, is an intravenous combination of sulbactam, a β -lactam antibiotic, and durlobactam, a novel broad-spectrum β -lactamase inhibitor that we are developing for the treatment of pneumonia and bloodstream infections caused by carbapenem-resistant *Acinetobacter baumannii* (“*Acinetobacter*”). Based on current carbapenem resistance rates, we estimate there are in excess of 200,000 hospital-treated carbapenem-resistant *Acinetobacter* infections annually across the United States, Europe, the Middle East and China for which significant morbidity and mortality exists due to limited treatment options. We initiated ATTACK (*Acinetobacter* Treatment Trial Against Colistin), our single Phase 3 registrational trial, in April 2019 and announced completion of trial enrollment in July 2021, with top-line data readout expected in the early fourth quarter of 2021.

Our second late-stage product candidate, zoliflodacin, is a novel orally administered molecule being developed for the treatment of uncomplicated gonorrhea. The bacterial pathogen responsible for gonorrhea is *Neisseria gonorrhoeae* (“*N. gonorrhoeae*”) including multidrug-resistant strains. Intramuscular injections of ceftriaxone now represent the only U.S. Centers for Disease Control and Prevention-recommended treatment option for the estimated 1.6 million annual cases of gonorrhea in the United States. We believe there is a growing unmet need for a single-dose oral antibiotic that will reliably treat patients with gonorrhea, including infections caused by multidrug-resistant strains of *N. gonorrhoeae*, which are emerging globally. The Phase 3 registrational trial, initiated in September 2019, is a multi-center, open-label, noninferiority trial in approximately 1,000 enrolled patients with uncomplicated gonorrhea. Our nonprofit collaborator, the Global Antibiotic Research and Development Partnership, is the sponsor of the registrational trial and is responsible for all trial expenses.

We are also developing ETX0282CPDP for the treatment of complicated urinary tract infections, including those caused by multidrug-resistant *Enterobacteriaceae*. ETX0282CPDP is an oral combination of ETX0282 with cefpodoxime proxetil. We believe there is a significant unmet need for new oral antibiotics to reliably treat the estimated 3 to 4 million patients diagnosed annually with complicated urinary tract infections. We have reported preliminary Phase 1 trial results, and subsequently demonstrated that an extended release tablet formulation achieved preclinical proof-of-concept of the desired pharmacokinetic profile both *in vitro* and in non-human primates. Having successfully completed the initial Phase 1 studies and preclinical work to deliver a formulation with the desired extended release profile, we are currently prioritizing our resources on completing the ATTACK trial and supporting the ongoing Phase 3 registrational trial for zoliflodacin, while we evaluate options for further clinical development of ETX0282CPDP.

Lastly, we are advancing development of a novel class of antibiotics, non β -lactam inhibitors of penicillin-binding proteins or NBPs. We believe NBPs constitute a potential new class of Gram-negative antibacterial agents that are designed to target a broad spectrum of multidrug resistant bacterial pathogens that overcome the main source of β -lactam resistance which is driven by β -lactamase activity. This novel class of agent is designed to target a broad spectrum of multidrug resistant bacterial pathogens that are part of the U.S. Centers for Disease Control and Prevention/World Health Organization list of high unmet medical needs. We selected ETX0462 as the initial clinical candidate for this program, based on demonstrated

activity against multiple Gram-negative pathogens including *Pseudomonas aeruginosa* and a number of high-priority biothreat pathogens, combined with a strong preclinical safety profile and attractive physiochemical properties. We currently are working toward completing the required pre-clinical activities to enable the program to advance into a Phase 1 clinical trial.

Arrangements with Innoviva

Since April 22, 2020, we have completed three private placement transactions pursuant to which we have sold Innoviva and its affiliates 28,672,897 shares of our common stock and warrants to purchase an additional 28,672,897 shares of our common stock with a weighted average exercise price of approximately \$2.35 per share. As a result of these transactions, as of the date of this prospectus supplement, Innoviva and its affiliates own approximately 60.6% of our outstanding common stock and, assuming full exercise of its warrants, have beneficial ownership of approximately 75.5% of our common stock. We have filed registration statements under the Securities Act to register the resale by Innoviva and its affiliates of the shares of common stock and warrants that we have issued to them, as well as the resale of the shares of our common stock that are issuable upon the exercise of such warrants.

In connection with the initial private placement we and Innoviva entered into an Investor Rights Agreement, dated April 22, 2020 (the "Investor Rights Agreement"). Under the Investor Rights Agreement, unless Innoviva waives its rights, if we propose to issue, offer or sell any equity securities, debt securities or rights, options or warrants to purchase such securities, we must first provide notice to Innoviva and allow it to participate in the proposed offering on the same terms and at up to the amount required to allow it to maintain its percentage ownership of our common stock on a fully diluted basis. If we inform Innoviva of our intention to sell securities and Innoviva does not elect to participate within 20 days, we would be free to sell any securities that Innoviva has not elected to purchase during the subsequent 120-day period, at a sale price not less than, and on other terms no less favorable to the us than, those we described to Innoviva in the notice.

The Investor Rights Agreement also provides that, for so long as Innoviva and its affiliates hold at least 15% of our outstanding shares of common stock on a fully diluted basis, Innoviva will have the right to designate two directors to our board of directors, and for so long as Innoviva and its affiliates hold at least 8% of our outstanding shares of common stock on a fully diluted basis, Innoviva will have the right to designate one director to our board of directors, subject to certain qualifications and conditions in the Investor Rights Agreement. As of the date of this prospectus supplement, Innoviva has not exercised its ability to appoint directors.

Corporate Information

We were incorporated under the laws of the State of Delaware in March 2018. Our principal executive offices are located at 35 Gatehouse Drive, Waltham, Massachusetts 02451 and our telephone number is (781) 810-0120. Our corporate website address is www.entasistx.com. Information contained on or accessible through our website is not part of this prospectus supplement or the accompany prospectus.

Implications of Being an Emerging Growth Company

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act"). For so long as we remain an emerging growth company ("EGC") we are permitted and intend to take advantage of specified reduced reporting requirements that are applicable to public companies, including:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;

- reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements; and
- not being required to hold a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We currently take advantage of some or all these reporting exemptions and we may continue to do so until we are no longer an EGC. Accordingly, the information that we provide stockholders may be different than the information you receive from other public companies in which you hold stock. We will remain an EGC until the earlier of (1) December 31, 2023, (2) the last day of the fiscal year in which we have total annual gross revenue of at least \$1.07 billion, (3) the last day of the fiscal year 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 June 30 of such fiscal year, and (4) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

Under Section 107(b) of the JOBS Act, an EGC can delay adopting new or revised accounting standards until those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

THE OFFERING	
Common stock offered by us	Shares of our common stock having an aggregate offering price of up to \$17,500,000.
Common stock to be outstanding after this offering	Assuming all \$17,500,000 of our common stock is sold in this offering at an assumed offering price of \$2.69 per share, which was the last reported sale price of our common stock on Nasdaq on August 26, 2021, we would have had 53,815,830 shares of common stock outstanding as of June 30, 2021. The actual number of shares issued will vary depending on the sales price under this offering.
Manner of offering	An “at the market offering” of shares of our common stock. The sale of shares of our common stock under this prospectus supplement, if any, may be made directly on Nasdaq, or through a market maker other than on an exchange. With our prior written consent, sales may also be made in negotiated transactions at market prices prevailing at the time of sale or at prices related to such prevailing market prices, or any other method permitted by law. See “Plan of Distribution” beginning on page S-10 of this prospectus supplement.
Sales agent	Cantor Fitzgerald & Co.
Use of Proceeds	We will use the net proceeds from the sale of shares of common stock by us under this prospectus supplement for working capital and general corporate purposes, including commercialization activities and funding our current and future clinical trials and preclinical studies. Pending use of the net proceeds of this offering as described above, we may invest the net proceeds in short-term, investment-grade, interest-bearing instruments. See “Use of Proceeds” on page S-7 of this prospectus supplement.
Risk Factors	Investing in our common stock involves a high degree of risk. See “Risk Factors” beginning on page S-5 of this prospectus supplement and under similar headings in the other documents that are incorporated by reference in this prospectus supplement and the accompanying prospectus for a discussion of factors to consider before deciding to purchase shares of our common stock.
Nasdaq listing	Our common stock is listed on The Nasdaq Global Market under the symbol “ETTX.”
Outstanding Shares	
The number of shares of common stock to be outstanding after this offering is based on 47,310,254 shares of our common stock outstanding as of June 30, 2021 and excludes, as of that date:	
<ul style="list-style-type: none"> • 32,672,897 shares of common stock issuable upon the exercise of outstanding warrants with a weighted-average exercise price of approximately \$2.39 per share; • 3,069,987 shares of common stock issuable upon the exercise of outstanding stock options under our 2018 Equity Incentive Plan and 2015 Stock Incentive Plan (before taking into account the results of the option exchange offer that we completed on July 16, 2021); • 949,700 unvested restricted stock units outstanding under our 2018 Equity Incentive Plan; 	

- 1,313,027 shares of common stock available for future grants under our 2018 Equity Incentive plan;
and
- 654,163 shares of common stock available for issuance under our 2018 Employee Stock Purchase Plan.

RISK FACTORS

Our business is subject to numerous risks. Prior to making a decision about investing in our shares of common stock, you should carefully consider the following risks, in addition to the risks described in the section entitled “Risk Factors” in Part I, Item 1A of our [Annual Report on Form 10-K for the year ended December 31, 2020](#) and in Part II, Item 1A of our Quarterly Reports on Form 10-Q for the quarters ended [March 31, 2021](#) and [June 30, 2021](#), and as may be described in our future filings with the SEC, which are incorporated by reference in this prospectus supplement and the accompanying prospectus. You should also carefully consider the other information included or incorporated by reference in this prospectus supplement, the accompanying prospectus and any free writing prospectus. Each of the risks described in these documents could materially and adversely affect our business, financial condition, results of operations and prospects, and could result in a partial or complete loss of your investment.

Risks Related to this Offering

Our stock price has been and may continue to be highly volatile, and the value of an investment in our common stock may decline.

During the 12-month period ended June 30, 2021, our stock traded as high as \$4.25 per share and as low as \$1.58 per share. The trading price of our common stock is likely to continue to be highly volatile and could be subject to wide fluctuations in response to several factors, some of which are beyond our control. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated or disproportionate to the operating performance of publicly traded companies. Broad market and industry factors may cause the market price and demand for our common stock to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from selling their shares of our common stock at or above the price paid for the shares and may otherwise negatively affect the liquidity of our common stock. In addition, in the past, following periods of volatility in the overall market and the market price of a particular company’s securities, securities class action litigation has often been instituted against these companies. This litigation, if instituted against us, could result in substantial costs and a diversion of our management’s attention and resources.

You will experience immediate and substantial dilution in the book value per share of the common stock you purchase.

The shares sold in this offering, if any, will be sold from time to time at various prices; however, the assumed offering price of our common stock is substantially higher than the as adjusted net tangible book value per share of our common stock. Therefore, investors purchasing shares of our common stock in this offering will pay a price per share that substantially exceeds the as adjusted net tangible book value per share after this offering. Assuming that an aggregate of 6,505,576 shares of our common stock are sold at an assumed offering price of \$2.69 per share, the last reported sale price of our common stock on Nasdaq on August 26, 2021, for aggregate gross proceeds of \$17,500,000, and after deducting commissions and estimated offering expenses payable by us, new investors in this offering will experience immediate dilution of \$1.39 per share, representing the difference between the assumed offering price and our as adjusted net tangible book value per share of the common stock you purchase in this offering. 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. In addition, we have a significant number of options and restricted stock units outstanding. If the holders of these securities exercise them or become vested in them, as applicable, you may incur further dilution.

The actual number of shares of common stock we will issue under the sales agreement, at any one time or in total, is uncertain.

Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver a sales notice to Cantor at any time throughout the term of the sales agreement. The number of shares that are sold by Cantor after we deliver a sales notice will fluctuate based on the market price of our common stock during the sales period and limits we set with Cantor. Because the price per share of

each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued.

Management will have broad discretion as to the use of proceeds from this offering and may invest or spend the proceeds in ways with which you do not agree and in ways that may not increase the value of your investment.

Our management will have broad discretion over the use of proceeds from the sale of shares of our common stock in this offering, including for any of the purposes described in the section of this prospectus entitled "Use of Proceeds," and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. You may not agree with our decisions, and our use of the proceeds may not yield any return on your investment. Our failure to apply the net proceeds from the sale of our shares in this offering could effectively have a material adverse effect on our business, delay the development of our products, compromise our ability to pursue our business strategy, and cause the price of our common stock to decline, and we might not be able to yield a significant return, if any, on our investment of these net proceeds. In addition, the net proceeds from the sale of our shares in this offering may not be sufficient for our anticipated uses, and we may need additional resources to progress our product candidates to the stage we expect.

Sales of a significant number of shares of our common stock in the public markets, or the perception that such sales could occur, could cause our stock price to decline.

Sales of a substantial number of shares of our common stock in the public markets, or the perception that such sales could occur, could depress the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities. It is possible that we could issue and sell additional shares of our common stock in the public markets. Furthermore, if our existing stockholders sell a large number of shares of our common stock, or the public market perceives that existing stockholders might sell shares of common stock, the market price of our common stock could decline significantly. Sales of substantial amounts of shares of our common stock in the public market by our executive officers, directors, 5% or greater stockholders or other stockholders, or the prospect of such sales, could adversely affect the market price of our common stock. We cannot predict the effect that future sales of our common stock would have on the market price of our common stock.

USE OF PROCEEDS

The amount of proceeds from this offering will depend upon the number of shares of our common stock sold and the market price at which they are sold. There can be no assurance that we will be able to sell any shares under or fully utilize the sales agreement as a source of financing. If we were to sell shares at an assumed offering price equal to the closing price of our common stock on August 26, 2021 of \$2.69 per share, the maximum number of shares that we could sell is 6,505,576. We estimate that the offering expenses, other than the sales agent's commission, will be approximately \$300,000. If we were to sell 6,505,576 shares of common stock at the August 26, 2021 closing price, we would receive \$17,500,000 of gross proceeds, which would result in net proceeds of approximately \$16,675,000 after deduction of the sales agent's commission and our estimated offering expenses. The actual proceeds to us, if any, will vary.

We will use the net proceeds from the sale of shares of common stock by us under this prospectus supplement for working capital and general corporate purposes, including commercialization activities and funding our current and future clinical trials and preclinical studies. Our management will have broad discretion in the application of the net proceeds received from this offering. Pending use of the net proceeds of this offering as described above, we may invest the net proceeds in short-term, investment-grade, interest-bearing instruments.

The expected use of net proceeds from this offering reflects our intentions based on 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 expenditures may vary significantly depending on numerous factors.

DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted to the extent of the difference between the price per share you pay in this offering and our as adjusted net tangible book deficit per share after this offering. We calculate net tangible book deficit per share by dividing our net tangible book deficit, which is tangible assets less total liabilities, by the number of outstanding shares of our common stock.

Our net tangible book value as of June 30, 2021 was approximately \$53.1 million, or \$1.12 per share. Net tangible book value per share after this offering gives effect to the sale of \$17,500,000 of common stock in this offering at an assumed offering price of \$2.69 per share, which was the closing price of our common stock as reported on Nasdaq on August 26, 2021, after deducting offering commissions and estimated expenses payable by us. Our net tangible book value as of June 30, 2021, after giving effect to this offering as described above, would have been approximately \$69.7 million, or \$1.30 per share of common stock. This represents an immediate increase in net tangible book value of \$0.18 per share to existing stockholders and an immediate dilution of \$1.39 per share to new investors purchasing our common stock in this offering. The following table illustrates the per share dilution:

Assumed offering price per share	\$2.69
Net tangible book value per share as of June 30, 2021	\$1.12
Increase in net tangible book value per share attributable to new investors purchasing our common stock in this offering	<u>\$0.18</u>
As adjusted net tangible book value per share as of June 30, 2021, after giving effect to this offering	<u>\$1.30</u>
Dilution per share to new investors in this offering	<u>\$1.39</u>

The table above assumes for illustrative purposes that an aggregate of 6,505,576 shares of our common stock are sold pursuant to this prospectus supplement and the accompanying prospectus at a price of \$2.69 per share, which was the last reported sale price of our common stock on Nasdaq on August 26, 2021, for aggregate gross proceeds of \$17,500,000. The shares sold in this offering, if any, will be sold from time to time at various prices.

An increase of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$2.69 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$17,500,000 is sold at that price, would result in a pro forma net tangible book value per share, as adjusted, after the offering of \$1.34 per share and would increase the dilution in net tangible book value per share to new investors in this offering to \$2.35 per share, after deducting commissions and estimated aggregate offering expenses payable by us. A decrease of \$1.00 per share in the price at which the shares are sold from the assumed offering price of \$2.69 per share shown in the table above, assuming all of our common stock in the aggregate amount of \$17,500,000 is sold at that price, would result in a pro forma net tangible book value per share, as adjusted, after the offering of \$1.21 per share and would decrease the dilution in net tangible book value per share to new investors in this offering to \$0.48 per share, after deducting commissions and estimated aggregate offering expenses payable by us.

The above discussion and table are based on 47,310,254 shares of our common stock outstanding as of June 30, 2021 and excludes, as of that date:

- 32,672,897 shares of common stock issuable upon the exercise of outstanding warrants with a weighted-average exercise price of approximately \$2.39 per share;
- 3,069,987 shares of common stock issuable upon the exercise of outstanding stock options under our 2018 Equity Incentive Plan and 2015 Stock Incentive Plan (before taking into account the results of the option exchange offer that we completed on July 16, 2021);
- 949,700 unvested restricted stock units outstanding under our 2018 Equity Incentive Plan;
- 1,313,027 shares of common stock available for future grants under our 2018 Equity Incentive plan; and

- 654,163 shares of common stock available for issuance under our 2018 Employee Stock Purchase Plan.

To the extent that any of the outstanding warrants or options are exercised or restricted stock units are vested and settled, there may be further dilution to investors participating in this offering. In addition, we may choose to raise additional capital because of market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans. If we raise additional capital through the sale of equity securities, the issuance of these securities could result in further dilution to our stockholders.

PLAN OF DISTRIBUTION

On August 27, 2021, we entered into a Controlled Equity OfferingSM Sales Agreement with Cantor Fitzgerald & Co. In accordance with the terms of the sales agreement, we may issue and sell by means of this prospectus supplement and the accompanying prospectus shares of our common stock having an aggregate gross sales price of up to \$17,500,000 from time to time through Cantor, acting as agent. A copy of the sales agreement is filed as an exhibit to our Current Report on Form 8-K filed on August 27, 2021 and is incorporated by reference in this prospectus supplement.

Upon delivery of a placement notice and subject to the terms and conditions of the sales agreement, Cantor may sell our common stock by any method permitted by law deemed to be an “at the market offering” as defined in Rule 415(a)(4) promulgated under the Securities Act. We may instruct Cantor not to sell common stock if the sales cannot be effected at or above the price designated by us from time to time. We or Cantor may suspend the offering of common stock upon notice and subject to other conditions.

We will pay Cantor commissions, in cash, for their services in acting as agent in the sale of our common stock. Cantor will be entitled to compensation at a fixed commission rate equal to 3.0% of the gross proceeds from each sale of our common stock. Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time. Pursuant to the sales agreement, we have also agreed to reimburse the sales agent for the fees and disbursements of its legal counsel in an amount not to exceed \$75,000. We estimate that the total expenses for the offering will be approximately \$300,000, excluding the sales agent’s commission.

Settlement for sales of common stock will occur on the second business day following the date on which any sales are made, or on some other date that is agreed upon by us and Cantor in connection with a particular transaction, in return for payment of the net proceeds to us. Sales of our common stock as contemplated in this prospectus supplement will be settled through the facilities of The Depository Trust Company or by such other means as we and Cantor may agree upon. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

Cantor will use its commercially reasonable efforts, consistent with its sales and trading practices, to sell on our behalf shares of our common stock as designated by us. In connection with the sale of the common stock on our behalf, Cantor will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation of Cantor will be deemed to be underwriting commissions or discounts. We have agreed to provide indemnification and contribution to Cantor against certain civil liabilities, including liabilities under the Securities Act.

The offering of our common stock pursuant to the sales agreement will terminate upon the termination of the sales agreement as permitted therein. We and Cantor may each terminate the sales agreement at any time upon ten days’ prior notice, and the sales agreement may also be terminated by Cantor at any time in certain circumstances, including the occurrence of a material and adverse change in our business or financial condition that makes it impractical or inadvisable to market our common stock or to enforce contracts for the sale of our common stock.

Cantor and its affiliates may in the future provide various investment banking, commercial banking and other financial services for us and our affiliates, for which services they may in the future receive customary fees. To the extent required by Regulation M, Cantor will not engage in any market making activities involving our common stock while the offering is ongoing under this prospectus.

This prospectus supplement and the accompanying prospectus in electronic format may be made available on a website maintained by Cantor and Cantor may distribute this prospectus electronically.

LEGAL MATTERS

The validity of the common stock offered by this prospectus supplement will be passed upon for us by Covington & Burling LLP. Certain corporate legal matters in connection with this offering will be passed upon for Cantor by Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C.

EXPERTS

The consolidated financial statements of Entasis Therapeutics Holdings Inc. as of December 31, 2020 and 2019, and for the years then ended, have been incorporated by reference herein in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at www.sec.gov. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K, including any amendments to those reports, proxy and information statements and other information that we file with or furnish to the SEC pursuant to Section 13(a) or 15(d) of the Exchange Act can also be accessed free of charge on our website at www.entasistx.com under "Investors & Media — SEC Filings." These filings will be available as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information contained in or accessible through our website does not constitute a part of, and is not incorporated into, this prospectus.

We have filed with the SEC a Registration Statement on Form S-3 (File No. 333-234041) under the Securities Act, of which this prospectus supplement forms a part. The rules and regulations of the SEC allow us to omit from this prospectus supplement certain information included in the registration statement. For further information about us and the securities we are offering under this prospectus supplement, you should refer to the registration statement and the exhibits and schedules filed with the registration statement. With respect to the statements contained in this prospectus supplement regarding the contents of any agreement or any other document, in each instance, the statement is qualified in all respects by the complete text of the agreement or document, a copy of which has been filed as an exhibit to the registration statement or an item incorporated by reference in the registration statement. You can obtain a copy of the registration statement, at prescribed rates, from the SEC at the address listed above. The registration statement and the documents referred to below under "Incorporation by Reference" are also available on our website, www.entasistx.com. We have not incorporated by reference into this prospectus supplement or the accompanying prospectus the information on, or that can be accessed through, our website, and you should not consider it to be a part of this prospectus supplement or the accompanying prospectus.

INCORPORATION OF INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" into this prospectus supplement the information we file with it, which means that we can disclose important information to you by referring you to those documents. The information which we incorporate by reference is an important part of this prospectus supplement and the accompanying prospectus, and certain information that we file later with the SEC will automatically update and supersede this information.

We incorporate by reference herein the following documents that we have previously filed with the SEC (File No. 001-38670):

- our Annual Report on Form 10-K for the year ended December 31, 2020, filed with the SEC on [March 23, 2021](#), as subsequently amended on [April 30, 2021](#);
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2021 and June 30, 2021, filed with the SEC on [May 5, 2021](#) and [August 12, 2021](#), respectively;
- our Current Reports on Form 8-K filed with the SEC on [May 3, 2021](#), [June 11, 2021](#) and [August 27, 2021](#); and

- the description of our Common Stock contained in [Exhibit 4.3 to our Annual Report on Form 10-K for the year ended December 31, 2019, filed with the SEC on March 11, 2020](#), including any amendments or reports filed for the purposes of updating this description.

In addition, all reports and other documents that we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, but excluding any information furnished to, rather than filed with, the SEC, will be deemed to be incorporated by reference into this prospectus supplement and the accompanying prospectus and deemed to be part of this prospectus supplement and the accompanying prospectus from the time of the filing of such reports and documents.

This prospectus supplement and the accompanying prospectus as further supplemented may contain information that updates, modifies or is contrary to information herein or in one or more of the documents incorporated by reference in this prospectus supplement or the accompanying prospectus. We have not authorized anyone else to provide you with different information. We take no responsibility for, and can provide no assurance as to the reliability of, any information that others may give. You should not assume that the information in this prospectus supplement and the accompanying prospectus is accurate as of any date other than the date of this prospectus supplement, the date of the accompanying prospectus or the date of the documents incorporated by reference in this prospectus supplement and the accompanying prospectus, respectively.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus but not delivered with the prospectus, including exhibits that are specifically incorporated by reference into such documents. You should direct any requests for documents to Entasis Therapeutics Holdings Inc., Attn: Elizabeth M. Keiley, General Counsel, 35 Gatehouse Drive, Waltham, Massachusetts 02451; telephone: (781) 810-0120.

PROSPECTUS



\$125,000,000

**Common Stock
Preferred Stock
Debt Securities
Warrants**

From time to time, we may offer up to \$125,000,000 of any combination of the securities described in this prospectus in one or more offerings. We may also offer securities as may be issuable upon conversion, redemption, repurchase, exchange or exercise of any securities registered hereunder, including any applicable antidilution provisions.

This prospectus provides a general description of the securities we may offer. Each time we offer securities, we will provide specific terms of the securities offered in a supplement 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 any documents incorporated by reference, before you invest in any of the securities being offered.

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

Our common stock is listed on The Nasdaq Global Market, or Nasdaq, under the symbol "ETTX." On September 27, 2019, the last reported sale price of our common stock was \$6.15 per share. The applicable prospectus supplement will contain information, where applicable, as to any other listing on Nasdaq or any securities market or other exchange of the securities, if any, covered by the prospectus supplement.

We will sell these securities directly to investors, through agents designated from time to time or to or through underwriters or dealers, on a continuous or delayed basis. For additional information on the methods of sale, you should refer to the section titled "Plan of Distribution" in this prospectus. If any agents or underwriters are involved in the sale of any securities with respect to which this prospectus is being delivered, the names of such agents or underwriters and any applicable fees, commissions, discounts or 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.

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 any related free writing prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus as described on page 6 of 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 17, 2019.

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ABOUT THIS PROSPECTUS

This prospectus is a part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. Under this shelf registration process, we may sell any combination of the securities described in this prospectus in one or more offerings up to a total aggregate offering price of \$125,000,000. This prospectus provides you with a general description of the securities we may offer.

Each time we sell securities under this prospectus, we will provide a prospectus supplement that will contain 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. The 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 any documents that we have incorporated by reference into this prospectus. You should read this prospectus, any applicable prospectus supplement and any related free writing prospectus, together with the information incorporated herein by reference as described under the heading “Incorporation of Certain Information by Reference,” before investing in any of the securities offered.

THIS PROSPECTUS MAY NOT BE USED TO CONSUMMATE A SALE OF SECURITIES UNLESS IT IS ACCOMPANIED BY A PROSPECTUS SUPPLEMENT.

Neither we, nor any agent, underwriter or dealer has authorized any person to give any information or to make any representation other than those contained or incorporated by reference in this prospectus, any applicable prospectus supplement or any related free writing prospectus prepared by or on behalf of us or to which we have referred you. This prospectus, any applicable supplement to this prospectus or any related free writing prospectus do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the registered securities to which they relate, nor do this prospectus, any applicable supplement to this prospectus or any related free writing prospectus constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any person to whom it is unlawful to make such offer or solicitation in such jurisdiction.

You should not assume that the information contained in this prospectus, any applicable prospectus supplement or any related free writing prospectus is accurate on any date subsequent to the date set forth on the front of the document or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus, any applicable prospectus supplement or any related free writing prospectus is delivered, or securities are sold, on a later date.

This prospectus and the information incorporated herein by reference 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 heading “Where You Can Find More Information.”

SUMMARY

The following summary highlights information contained elsewhere in this prospectus. This summary is not complete 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 consolidated financial statements, and the exhibits to the registration statement of which this prospectus is a part.

Unless the context indicates otherwise, references in this prospectus to “Entasis,” “the Company,” “we,” “us,” “our” and similar references refer to Entasis Therapeutics Holdings Inc. and its wholly owned subsidiaries.

Company Overview

We are a clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of novel antibacterial products to treat serious infections caused by multidrug-resistant Gram-negative bacteria. Leveraging our targeted-design platform, we have engineered and developed product candidates that target clinically validated mechanisms to address antibiotic resistance. Our lead product candidate, durlobactam (formerly ETX2514), as well as one of our other product candidates, ETX0282, inhibit one of the most prevalent forms of bacterial resistance, β -lactamase enzymes, so-named because of their ability to inactivate β -lactam antibiotics, one of the most commonly used classes of antibiotics. By blocking this resistance mechanism, these product candidates, when administered in combination with β -lactam antibiotics, are designed to restore the efficacy of those antibiotics. Our other product candidate, zoliflodacin, targets the validated mechanism of action of the fluoroquinolone class of antibiotics, but does so in a novel manner to avoid existing fluoroquinolone resistance.

SUL-DUR (formerly ETX2514SUL) is a fixed-dose combination of sulbactam, an intravenous β -lactam antibiotic, with durlobactam, a novel broad-spectrum intravenous β -lactamase inhibitor, or BLI, that we are developing for the treatment of a variety of serious multidrug-resistant infections caused by *Acinetobacter baumannii*, or *Acinetobacter*. Based on a series of discussions with the U.S. Food and Drug Administration, or FDA, including an end-of-Phase-2 meeting, we initiated the single Phase 3 clinical trial in April 2019, with data expected in the second half of 2020.

Zoliflodacin is a novel orally administered molecule that inhibits bacterial gyrase, an essential enzyme in bacterial reproduction, targeting *Neisseria gonorrhoeae*, the bacterial pathogen responsible for gonorrhea. Intramuscular ceftriaxone now represents the last-resort treatment option for gonorrhea, although resistant strains are beginning to emerge. We believe that there is a growing unmet need for an oral antibiotic, that will reliably treat patients with gonorrhea, including multidrug-resistant gonorrhea. The Phase 3 clinical trial will be funded and initiated by our nonprofit collaborator, the Global Antibiotic Research and Development Partnership, or GARDP, in 2019 with data expected in 2021.

We are also developing ETX0282CPDP for the treatment of complicated UTIs, including those caused by extended-spectrum β -lactamase, or ESBL, producing bacterial strains or carbapenem-resistant *Enterobacteriaceae*, or CRE. ETX0282CPDP is an oral, fixed dose combination of ETX0282, a novel oral BLI, with cefpodoxime proxetil, an oral β -lactam antibiotic. We believe there is a significant unmet need for new oral antibiotics that reliably treat patients with multidrug-resistant Gram-negative infections. We initiated a multi-part Phase 1 clinical trial of ETX0282CPDP in Australia in the second quarter of 2018 and reported initial preliminary results in June 2019. Additional Phase 1 work is ongoing with efforts to formulate ETX0282 for further clinical development.

We are using our targeted-design platform in an attempt to develop a novel class of antibiotics, non β -lactam inhibitors of the penicillin binding proteins, or NBPs. Penicillin binding proteins, or PBPs, are clinically validated targets of β -lactam antibiotics, such as penicillins and carbapenems. Due to their differentiated chemical structure, our NBPs are not subject to inactivation by β -lactamases, unlike β -lactam

antibiotics. Accordingly, we believe our NBPs constitute a potential new class of Gram-negative antibacterial agents with no pre-existing resistance that are designed to target a broad spectrum of pathogens, including *Pseudomonas aeruginosa*, or *Pseudomonas*. We expect to select an initial clinical candidate from our NBP program in 2019.

Our Pipeline

The following table summarizes the status of our product candidates and preclinical program, which have all been developed using our targeted-design platform:

Product Candidate	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Upcoming Milestones	Commercial Rights	Partnerships
Sulbactam-durlobactam IV	Multi-drug resistant <i>Acinetobacter</i> infections					<ul style="list-style-type: none"> Ongoing Phase 3 trial; data expected 2H 2020 	Worldwide excluding Asia-Pacific ⁽¹⁾	
Zoliflodacin Oral	Uncomplicated gonorrhea					<ul style="list-style-type: none"> Phase 3 trial initiated Sept. 2019; data 2021 	All developed countries ⁽²⁾	
ETX0282CPDP Oral	Complicated UTIs (<i>Enterobacteriaceae</i> including ESBL-producing and CRE)					<ul style="list-style-type: none"> Post Phase 1 formulation efforts initiated in 2019 	Worldwide	
NBP Program⁽³⁾ IV	Gram-negative infections (initially multi-drug resistant <i>Pseudomonas</i>)					<ul style="list-style-type: none"> Select initial clinical candidate in 2019 	Worldwide	

(1) Zai Lab has licensed Asia-Pacific rights to SUL-DUR.

(2) GARDP will fully fund the Phase 3 development program and has commercial rights in low-income and specified middle-income countries. Entasis has retained commercial rights in all major markets in North America, Europe and Asia-Pacific.

(3) Non-β-lactam inhibitors of the penicillin-binding protein.

Corporate Information

Entasis Therapeutics Holdings Inc. was incorporated under the laws of the State of Delaware in March 2018. Our shares are listed on the Nasdaq Global Market, where our trading symbol is ETTX. Our principal executive offices are located at 35 Gatehouse Drive, Waltham, Massachusetts 02451 and our telephone number is (781) 810-0120. Information contained on or accessible through our website is not incorporated by reference into this prospectus, and you should not consider such information as part of this prospectus or in deciding whether to purchase our securities.

Solely for convenience, trademarks and trade names referred to, including logos, artwork and other visual displays, may appear without the ® or TM symbols, but such references are not intended to indicate, in any way, that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend our use or display of other companies' trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

Implications of Being an Emerging Growth Company and a Smaller Reporting Company

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For so long as we remain an emerging growth company, or EGC, we are permitted and intend to take advantage of specified reduced reporting requirements that are applicable to public companies, including:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;

- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation in our periodic reports, proxy statements and registration statements; and
- not being required to hold a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We currently take advantage of some or all these reporting exemptions and we may continue to do so until we are no longer an EGC. Accordingly, the information that we provide stockholders may be different than the information you receive from other public companies in which you hold stock. We will remain an EGC until the earlier of (1) December 31, 2023, (2) the last day of the fiscal year in which we have total annual gross revenue of at least \$1.07 billion, (3) the last day of the fiscal year 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 June 30 of such fiscal year, and (4) the date on which we have issued more than \$1.0 billion in non-convertible debt during the prior three-year period.

Under Section 107(b) of the JOBS Act, an EGC can delay adopting new or revised accounting standards until those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We are also a smaller reporting company as defined in the Securities Exchange Act of 1934, as amended, or the Exchange Act. We may continue to be a smaller reporting company even after we are no longer an emerging growth company. We may take advantage of certain of the scaled disclosures available to smaller reporting companies and will be able to take advantage of these scaled disclosures for so long as (i) our voting and non-voting common stock held by nonaffiliates is less than \$250.0 million as of June 30 of such fiscal year or (ii) our annual revenue is less than \$100.0 million during the most recently completed fiscal year and our voting and non-voting common stock held by non-affiliates is less than \$700.0 million measured as of June 30 of such fiscal year.

The Securities We May Offer

We may offer shares of our common stock and preferred stock, various series of debt securities and warrants to purchase any of such securities, up to a total aggregate offering price of \$125,000,000 from time to time in one or more offerings under this prospectus, together with any applicable prospectus supplement and any related free writing prospectus, at prices and on terms to be determined by market conditions at the time of the relevant 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, exchange or sinking fund terms;
- ranking;
- restrictive covenants;

- voting or other rights;
- conversion or exchange prices or rates and 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
- important U.S. federal income tax considerations.

The 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.

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

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

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

Common Stock. We may issue shares of our common stock from time to time. Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders and does not have cumulative voting rights. Subject to preferences that may apply to any outstanding preferred stock, holders of our common stock are entitled to receive ratably any dividends that our board of directors may declare out of funds legally available for that purpose. In the event of our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preference of any outstanding preferred stock. Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate in the future. In this prospectus, we have summarized certain general features of our common stock under the heading “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. Under our certificate of incorporation, our board of directors has the authority, without further action by our stockholders (unless such stockholder action is required by applicable law or the rules of any stock exchange or market on which our securities are then traded), to issue up to 10,000,000 shares of preferred stock in one or more series and to fix the number, rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences and 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 common stock. Any convertible preferred stock we may issue will be convertible into our common stock or exchangeable for our other securities. Conversion may be mandatory or at the holder’s 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 the heading “Description of Capital Stock — Preferred Stock.” 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 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 the holder’s 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 party, as trustee. In this prospectus, we have summarized certain general features of the debt securities under the heading “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 and any supplemental indentures that contain the terms of the debt securities. We have filed a form of indenture as an exhibit to the registration statement of which this prospectus is a part. We will file as exhibits to the registration statement of which this prospectus is a part, or will incorporate by reference from reports that we file with the SEC, supplemental indentures and forms of debt securities containing the terms of the debt securities being offered.

Warrants. We may issue warrants for the purchase of common stock, preferred stock or debt securities, from time to time, in one or more series. We may issue warrants independently or in combination with common stock, preferred stock or debt securities. In this prospectus, we have summarized certain general features of the warrants under the heading “Description of Warrants.” 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 particular series of warrants being offered, as well as the complete warrant agreements and warrant certificates that contain the terms of the warrants. We have filed forms of the warrant agreements and forms of warrant certificates containing the terms of the warrants that we may offer as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits 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 warrant or the warrant agreement and warrant certificate, as applicable, that contain the terms of the particular series of warrants we are offering, and any supplemental agreements, before the issuance of such warrants.

Any warrants issued under this prospectus may be evidenced by warrant certificates. Warrants may be issued under an applicable warrant agreement that we enter into with a warrant agent. We will indicate the name and address of the warrant agent, if applicable, in the prospectus supplement relating to the particular series of warrants being offered.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully review the risks and uncertainties described under the heading “Risk Factors” contained in the applicable prospectus supplement and any related free writing prospectus, and under similar headings in our [Annual Report on Form 10-K for the year ended December 31, 2018](#), and in our most recent [Quarterly Report on Form 10-Q](#), as updated by our subsequent filings, which are incorporated by reference into this prospectus, before deciding whether to purchase any of the securities being registered pursuant to the registration statement of which this prospectus is a part. Each of the risk factors could adversely affect our business, results of operations, financial condition and cash flows, as well as adversely affect the value of an investment in our securities, and the occurrence of any of these risks might cause you to lose all or part of your investment. Additional risks not presently known to us or that we currently believe are immaterial may also significantly impair our business operations.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference in this prospectus contain forward-looking statements. These are based on our management’s current beliefs, expectations and assumptions about future events, conditions and results and on information currently available to us. Discussions containing these forward-looking statements may be found, among other places, in the sections titled “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 our most recent [Quarterly Report on Form 10-Q](#), as well as any amendments thereto, filed with the SEC.

In some cases, you can identify forward-looking statements by terminology such as “anticipate,” “believe,” “could,” “estimate,” “expects,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would” or the negative or plural of those terms, and similar expressions intended to identify statements about the future, although not all forward-looking statements contain these words. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements.

Any statements in this prospectus, or incorporated herein by reference, about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and are forward-looking statements. Within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act these forward-looking statements include statements regarding:

- our plans to develop and commercialize our product candidates;
- our planned clinical trials for our product candidates;
- the timing of the availability of data from our clinical trials;
- the timing of our selection of an initial clinical candidate from our NBP program;
- our expectation that the efficacy and safety data from our planned and ongoing Phase 3 trials, if positive, will be sufficient to support submission of an NDA to the FDA;
- our ability to obtain grants or other government funding to develop our product candidates;
- our ability to take advantage of benefits offered by current and pending legislation related to the development of products addressing antimicrobial resistance;
- the timing of our planned regulatory filings;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the clinical utility of our product candidates and their potential advantages compared to other treatments;
- our commercialization, marketing and distribution capabilities and strategy;
- our ability to establish and maintain arrangements for the manufacture of our product candidates;
- our ability to establish and maintain collaborations and to recognize the potential benefits of such collaborations;
- our estimates regarding the market opportunities for our product candidates;
- our intellectual property position and the duration of our patent rights; and
- our estimates regarding future expenses, capital requirements and needs for additional financing.

You should refer to the “Risk Factors” section 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, for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Given these risks, uncertainties and other factors, many of which are beyond our control, we cannot assure you that the forward-looking statements in this prospectus will prove to be accurate, and you should not place undue

reliance on these forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to revise any forward-looking statements to reflect events or developments occurring after the date of this prospectus, even if new information becomes available in the future.

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds from the sale of the securities offered hereby. Except as described in any applicable prospectus supplement or in any free writing prospectuses that we may authorize to be provided to you in connection with a specific offering, we currently intend to use the net proceeds from the sale of the securities offered hereby, if any, to fund research and development of our product candidates, acquire or invest in businesses, products or technologies that are complementary to our own, although we have no current plans, commitments or agreements with respect to any acquisitions as of the date of this prospectus, and for working capital and general corporate purposes. We will set forth in the applicable prospectus supplement or free writing prospectus our intended use for the net proceeds received from the sale of any securities sold pursuant to the prospectus supplement or free writing prospectus. Pending the use of net proceeds, we intend to invest the net proceeds in short-term, investment-grade, interest-bearing obligations, certificates of deposit or direct or guaranteed obligations of the United States government.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock and provisions of our amended and restated certificate of incorporation and amended and restated bylaws are summaries. You should also refer to the amended and restated certificate of incorporation and the amended and restated bylaws, which are filed as exhibits to the registration statement of which this prospectus is part.

General

Under our amended and restated certificate of incorporation we are authorized to issue up to 125,000,000 shares of common stock, par value \$0.001 per share, and 10,000,000 shares of preferred stock, par value \$0.001 per share, all of which shares of preferred stock are undesignated. Our board of directors may establish the rights and preferences of the preferred stock from time to time. As of September 27, 2019, we had outstanding 13,134,538 shares of common stock.

Common Stock

Voting Rights

Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders. The affirmative vote of holders of at least 66²/₃% of the voting power of all of the then-outstanding shares of capital stock, voting as a single class, will be required to amend certain provisions of our amended and restated certificate of incorporation, including provisions relating to amending our amended and restated bylaws, the classified board, the size of our board, removal of directors, director liability, vacancies on our board, special meetings, stockholder notices, actions by written consent and exclusive forum.

Dividends

Subject to preferences that may apply to any outstanding preferred stock, holders of our common stock are entitled to receive ratably any dividends that our board of directors may declare out of funds legally available for that purpose on a non-cumulative basis.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of our common stock are entitled to share ratably in all assets remaining after payment of liabilities and the liquidation preference of any outstanding preferred stock.

Rights and Preferences

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

Preferred Stock

Pursuant to our amended and restated certificate of incorporation, our board of directors has the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series and to fix the number, rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences and 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 common stock. The issuance of our preferred stock could adversely affect the voting power of holders of 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, or make the removal of management more difficult. Additionally, the issuance of preferred stock may have the effect of decreasing the market price of the common stock.

Our board of directors will fix the designations, voting powers, preferences and rights of each series, as well as the qualifications, limitations or restrictions thereof, of the preferred stock of each series that we offer under this prospectus and applicable prospectus supplements 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 before the issuance of that series of preferred stock. This description will include:

- the title and stated value;
- the number of shares we are offering;
- the liquidation preference per share;
- the purchase price per share;
- the dividend rate per share, dividend period and payment dates and method of calculation for dividends;
- whether dividends will be cumulative or non-cumulative and, if cumulative, the date from which dividends will accumulate;
- our right, if any, to defer payment of dividends and the maximum length of any such deferral period;
- the procedures for any auction and remarketing, if any;
- the provisions for a sinking fund, if any;
- 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 or other securities of ours, including depositary shares and warrants, and, if applicable, the conversion period, the conversion price, or how it will be calculated, and under what circumstances it may be adjusted;
- whether the preferred stock will be exchangeable into debt securities, and, if applicable, the exchange period, the exchange price, or how it will be calculated, and under what circumstances it may be adjusted;
- voting rights, if any, of the preferred stock;
- preemption rights, if any;
- restrictions on transfer, sale or other assignment, if any;
- whether interests in the preferred stock will be represented by depositary shares;
- a discussion of any material or special U.S. 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;
- any limitations on issuances of any class or series of preferred stock ranking senior to or on a parity with the series of preferred stock being issued as to dividend rights and rights if we liquidate, dissolve or wind up our affairs; and
- any other specific terms, rights, preferences, privileges, qualifications or restrictions of the preferred stock.

The Delaware General Corporation Law, or DGCL, which is the law of the state of our incorporation, provides that the holders of preferred stock will have the right to vote separately as a class (or, in some cases, as a series) on an amendment to our certificate of incorporation if the amendment would change the par value, the powers, preferences or special rights of the class or series so as to adversely affect the class or series,

as the case may be, or, unless the certificate of incorporation provided otherwise, the number of authorized shares of the class. This right is in addition to any voting rights that may be provided for in the applicable certificate of designation.

Registration Rights

Certain holders of shares of our common stock have the right to demand that we file a registration statement or request that we cover their shares by a registration statement that we otherwise file, as described below.

Demand Registration Rights

The holders of at least 30% of registrable securities then outstanding (or a lesser percent if the anticipated aggregate offering price, net of selling expenses, would exceed \$15,000,000) may, on not more than one occasion, request that we register all or a portion of their shares, subject to certain specified exceptions.

Piggyback Registration Rights

If we propose to register any of our securities under the Securities Act, either for our own account or for the account of other security holders, the holders of all shares having “piggyback” registration rights are entitled to notice of the registration and allowed to include all or a portion of their shares of common stock in the registration, subject to specified conditions and limitations.

S-3 Registration Rights

One or more holders may, on not more than two occasions within any 12-month period, request that we register all or a portion of their shares on Form S-3 if we are qualified to file a registration statement on Form S-3, subject to specified exceptions. Such request for registration on Form S-3 must cover securities with an aggregate offering price which equals or exceeds \$3,000,000, net of selling expenses. The right to have such shares registered on Form S-3 is further subject to other specified conditions and limitations.

Other Provisions

In the event that any registration in which the holders of registrable shares participate pursuant to the investors’ rights agreement is an underwritten public offering, the number of registrable shares to be included may, in specified circumstances, be limited due to market conditions.

We will pay the registration expenses, other than underwriting discounts, selling commissions and stock transfer taxes, of up to \$50,000 for the shares registered pursuant to the demand, piggyback and Form S-3 registrations described above. The registration rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

The demand, piggyback and Form S-3 registration rights described above will expire no later than five years after the completion of our initial public offering, or with respect to any particular holder, at such time that such holder can sell all of its shares under Rule 144 of the Securities Act during any three-month period.

Anti-Takeover Provisions

Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws

Our amended and restated certificate of incorporation and amended and restated bylaws include a number of provisions that may deter or impede hostile takeovers or changes of control or management. These provisions include:

- **Issuance of Undesignated Preferred Stock.** Our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of preferred stock enables our board of directors to make it more difficult or to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise.
- **Classified Board.** Our amended and restated certificate of incorporation provides for a classified board of directors consisting of three classes of directors, with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. This provision may have the effect of delaying a change in control of our board.
- **Board of Directors Vacancies.** Our amended and restated certificate of incorporation and amended and restated bylaws authorize only our board of directors to fill vacant directorships. In addition, the number of directors constituting our board of directors may be set only by resolution adopted by a majority vote of our entire board of directors. These provisions prevent a stockholder from increasing the size of our board of directors and gaining control of our board of directors by filling the resulting vacancies with its own nominee.
- **Stockholder Action; Special Meetings of Stockholders.** Our amended and restated certificate of incorporation provides that our stockholders may not take action by written consent, but may only take action at annual or special meetings of our stockholders. Stockholders will not be permitted to cumulate their votes for the election of directors. Our amended and restated bylaws provide that special meetings of our stockholders may be called only by the chairman of our board of directors, our chief executive officer or president or by our board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors.
- **Advance Notice Requirements for Stockholder Proposals and Director Nominations.** Our amended and restated bylaws provide advance notice requirements for stockholders seeking to bring business before our annual meeting of stockholders, or to nominate candidates for election as directors at our annual meeting of stockholders. Our amended and restated bylaws also specify certain requirements as to the form and content of a stockholder's notice. These provisions may make it more difficult for our stockholders to bring matters before our annual meeting of stockholders or to nominate directors at annual meetings of stockholders.

We designed these provisions to enhance the likelihood of continued stability in the composition of our board of directors and its policies, to discourage certain types of transactions that may involve an actual or threatened acquisition of us, and to reduce our vulnerability to an unsolicited acquisition proposal. We also designed these provisions to discourage certain tactics that may be used in proxy fights. However, these provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, they may also reduce fluctuations in the market price of our shares that could result from actual or rumored takeover attempts.

Section 203 of the Delaware General Corporation Law

We are subject to Section 203 of the DGCL, which prohibits a Delaware corporation from engaging in any business combination with any interested stockholder for a period of three years after the date that such stockholder became an interested stockholder, with the following exceptions:

- before such date, the board of directors of the corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder;
- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction began, excluding for purposes of determining the voting stock outstanding, but not the outstanding voting stock owned by the interested stockholder, those shares owned (i) by persons who are directors and also officers and (ii) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or

- on or after such date, the business combination is approved by the board of directors and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66²/₃% of the outstanding voting stock that is not owned by the interested stockholder.

In general, Section 203 defines a “business combination” to include the following:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition of 10% or more of the assets of the corporation involving the interested stockholder;
- subject to certain exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- any transaction involving the corporation that has the effect of increasing the proportionate share of the stock or any class or series of the corporation beneficially owned by the interested stockholder; or
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits by or through the corporation.

In general, Section 203 defines an “interested stockholder” as an entity or person who, together with the entity or person’s affiliates and associates, beneficially owns, or is an affiliate or associate of the corporation and within three years prior to the time of determination of interested stockholder status did own, 15% or more of the outstanding voting stock of the corporation.

A Delaware corporation may “opt out” of these provisions with an express provision in its certificate of incorporation. We have not opted out of these provisions, which may as a result, discourage or prevent mergers or other takeover or change of control attempts of us.

Choice of Forum

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our certificate of incorporation or our bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. Our amended and restated certificate of incorporation further provides that the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. The enforceability of similar choice of forum provisions in other companies’ certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with one or more actions or proceedings described above, a court could find the choice of forum provisions contained in our amended and restated certificate of incorporation to be inapplicable or unenforceable.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A. The transfer agent’s address is P.O. Box 505000, Louisville, KY 40233-5000. 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 Nasdaq

Our common stock is listed on Nasdaq under the symbol “ETTX.”

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 prospectuses 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;
- 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;
- 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 applicable 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;
- 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.

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
- 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 the DTC, or another depository named by us and identified in the applicable 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 to any book-entry 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 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 of 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.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplement and in any related free writing prospectus that we may authorize to be distributed to you, summarizes the material terms and provisions of the warrants that we may offer under this prospectus, which may consist of warrants to purchase common stock, preferred stock or debt securities and may be issued in one or more series. Warrants may be offered independently or in combination with common stock, preferred stock or debt securities offered by any prospectus supplement. While the terms we have summarized below will apply generally to any warrants that we may offer under this prospectus, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. The following description of warrants will apply to the warrants offered by this prospectus unless we provide otherwise in the applicable prospectus supplement. The applicable prospectus supplement for a particular series of warrants may specify different or additional terms.

We have filed forms of the warrant agreements and forms of warrant certificates as exhibits to the registration statement of which this prospectus is a part. We will file as exhibits 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 warrant agreement, if any, including a form of warrant certificate, that contains the terms of the particular series of warrants we are offering, as well as any supplemental agreements, before the issuance of such warrants. The following summaries of material terms and provisions of the warrants are subject to, and qualified in their entirety by reference to, all the provisions of the form of warrant or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements applicable to a particular series of warrants that we may offer under this prospectus. We urge you to read the applicable prospectus supplement related to the particular series of warrants that we may offer under this prospectus, as well as any related free writing prospectus, and the complete form of warrant or the warrant agreement and warrant certificate, as applicable, and any supplemental agreements, that contain the terms of the warrants.

General

In the applicable prospectus supplement, we will describe the terms of the series of warrants being offered, including, to the extent applicable:

- the offering price or prices and aggregate number of warrants offered;
- the currency or currencies for which the warrants may be purchased;
- the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- the date on and after which the warrants and the related securities will be separately transferable;
- the minimum or maximum amount of such warrants which may be exercised at any one time;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable on exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased on such exercise;
- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable on the exercise of one warrant and the price at which, and the currency in which, these shares may be purchased on such exercise;
- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreements and the warrants;
- the terms of any rights to redeem or call the warrants;
- the terms of any rights to force the exercise of the warrants;
- any provisions for changes to or adjustments in the exercise price or number of securities issuable on exercise of the warrants;
- the dates on which the right to exercise the warrants will commence and expire;
- the manner in which the warrant agreements and warrants may be modified;

- a discussion of material or special U.S. federal income tax considerations of holding or exercising the warrants;
- the terms of the securities issuable on exercise of the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

Before exercising their warrants, holders of warrants will not have any of the rights of holders of the securities purchasable on such exercise, including:

- in the case of warrants to purchase common stock or preferred stock, the right to receive dividends, if any, or, payments upon our liquidation, dissolution or winding up or to exercise voting rights, if any; or
- in the case of warrants to purchase debt securities, the right to receive payments of principal of, or premium, if any, or interest on, the debt securities purchasable upon exercise or to enforce covenants in the applicable indenture.

Exercise of Warrants

Each warrant will entitle the holder to purchase the securities that we specify in the applicable prospectus supplement at the exercise price that we describe in the applicable prospectus supplement. The warrants may be exercised as described in the prospectus supplement relating to the warrants offered. Unless we otherwise specify in the applicable prospectus supplement, warrants may be exercised at any time up to the expiration date that we list in the applicable prospectus supplement. After the close of business on the expiration date, unexercised warrants will become void.

Unless we otherwise specify in the applicable prospectus supplement, holders of the warrants may exercise the warrants by delivering the warrant certificate representing the warrants to be exercised together with specified information, and paying the required amount to the warrant agent in immediately available funds, as provided in the applicable prospectus supplement. We will set forth on the reverse side of the warrant certificate and in the applicable prospectus supplement the information that the holder of the warrant will be required to deliver to the warrant agent in connection with the exercise of the warrant.

On receipt of the required payment and the warrant certificate properly completed and duly executed at the corporate trust office of the warrant agent, if any, or any other office, including ours, indicated in the applicable prospectus supplement, we will issue and deliver the securities purchasable on such exercise. If fewer than all of the warrants represented by the warrant certificate are exercised, then we will issue a new warrant certificate for the remaining amount of warrants. If we so indicate in the applicable prospectus supplement, holders of the warrants may surrender securities as all or part of the exercise price for warrants.

Governing Law

Unless we provide otherwise in the applicable prospectus supplement, the warrants and warrant agreements will be governed by and construed in accordance with the laws of the State of New York.

Enforceability of Rights by Holders of Warrants

Each warrant agent, if any, will act solely as our agent under the applicable warrant agreement and will not assume any obligation or relationship of agency or trust with any holder of any warrant. A single bank or trust company may act as warrant agent for more than one issue of warrants. A warrant agent will have no duty or responsibility in case of any default by us under the applicable warrant agreement or warrant, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand on us. Any holder of a warrant may, without the consent of the related warrant agent or the holder of any other warrant, enforce by appropriate legal action its right to exercise, and receive the securities purchasable on exercise of, its warrants.

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 or depositary 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. Global securities will be registered in the name of the depositary or its participants. Consequently, for global securities, 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 that are not issued in 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 such 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 or third party 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 holder, we have no further responsibility for the payment or notice even if that 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 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 an 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, the DTC, New York, New York, 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 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 as a global security, 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

As an indirect holder, an investor's rights relating to a global security will be governed by the account rules of the investor's financial institution and of the depositary, 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 depositary that holds the global security.

If securities are issued only as global securities, 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 or broker 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 the 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 depositary's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in the global security;
- we and any applicable trustee have no responsibility for any aspect of the depositary's actions or for its records of ownership interests in the global security, nor will we or any applicable trustee supervise the depositary in any way;
- the depositary may, and we understand that the DTC will, require that those who purchase and sell interests in the global security within its book-entry system use immediately available funds, and your broker or bank may require you to do so as well; and
- financial institutions that participate in the depositary's book-entry system, and through which an investor holds its interest in the 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, a global security will terminate and interests in it will be exchanged for physical certificates representing those interests. After that exchange, the choice of whether to hold securities directly or in street name will be up to the investor. Investors must consult their own banks or brokers to find out how to have their interests in securities transferred to their own names, 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 applicable 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 prospectus supplement. When a global security terminates, the depositary, and neither we nor 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 the securities from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities to or through underwriters or dealers, through agents, or directly to one or more purchasers. We may distribute securities from time to time in one or more transactions:

- at a fixed price or prices, which may be changed;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

We may also sell equity securities covered by this registration statement in an “at the market offering” as defined in Rule 415 under the Securities Act. Such offering may be made into an existing trading market for such securities in transactions at other than a fixed price, either:

- on or through the facilities of Nasdaq or any other securities exchange or quotation or trading service on which such securities may be listed, quoted or traded at the time of sale; and/or
- other than on Nasdaq or such other securities exchanges or quotation or trading services.

Such at the market offerings, if any, may be conducted by underwriters acting as principal or agent.

A prospectus supplement or supplements (and any related free writing prospectus that we may authorize to be provided to you) will describe the terms of the offering of the securities, including, to the extent applicable:

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

Only underwriters named in the prospectus supplement are underwriters of the securities offered by the prospectus supplement.

If underwriters are used in the sale, they will acquire the securities for their own account and may resell the securities from time to time in one or more transactions at a fixed public offering price or at varying prices determined at the time of sale. The obligations of the underwriters to purchase the securities will be subject to the conditions set forth in the applicable underwriting agreement. We may offer the securities to the public through underwriting syndicates represented by managing underwriters or by underwriters without a syndicate. Subject to certain conditions, the underwriters will be obligated to purchase all of the securities offered by the prospectus supplement. Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may change from time to time. We may use underwriters with whom we have a material relationship. We will describe in the prospectus supplement, naming the underwriter, the nature of any such relationship.

We may sell securities directly or through agents we designate from time to time. We will name any agent involved in the offering and sale of securities, and we will describe any commissions we will pay the agent in the prospectus supplement. Unless the prospectus supplement states otherwise, our agent will act on a best-efforts basis for the period of its appointment.

We may authorize agents or underwriters to solicit offers by certain types of institutional investors to purchase 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. We will describe the conditions to these contracts and the commissions we must pay for solicitation of these contracts in the prospectus supplement.

We may provide agents and underwriters with indemnification against civil liabilities related to this offering, including liabilities under the Securities Act, or contribution with respect to payments that the agents or underwriters may make with respect to these liabilities. Agents and underwriters may engage in transactions with, or perform services for, us in the ordinary course of business.

All securities we 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. Overallotment involves sales in excess of the offering size, which create a short position. Stabilizing transactions permit bids to purchase the underlying security so long as the stabilizing bids do not exceed a specified maximum. Short covering transactions involve purchases of the securities in the open market after the distribution is completed to cover short positions. 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 stabilizing or covering transaction to cover short positions. Those activities may cause the price of the securities to be higher than it would otherwise be. If commenced, the underwriters may discontinue any of the activities at any time. These transactions may be effected on any exchange or over-the-counter market or otherwise.

Any underwriters who are qualified market makers on Nasdaq may engage in passive market making transactions in the securities on Nasdaq 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. Passive market making may stabilize the market price of the securities at a level above that which might otherwise prevail in the open market and, if commenced, may be discontinued at any time.

LEGAL MATTERS

Unless otherwise indicated in the applicable prospectus supplement, certain legal matters in connection with the offering and the validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon by Cooley LLP. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of Entasis Therapeutics Holdings Inc. as of December 31, 2018 and 2017, and for the years then ended, have been incorporated by reference herein in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus is part of the registration statement on Form S-3 we filed with the SEC under the Securities Act. 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. You should rely only on the information contained in this prospectus or incorporated by reference. We have not authorized anyone else 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. The SEC maintains a website that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC, including Entasis. The address of the SEC website is www.sec.gov.

We maintain a website at www.entasistx.com. Information contained in or accessible through our website does not constitute a part of this prospectus.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is considered to be a part of this prospectus, and the information that we file later with the SEC will automatically update and, where applicable, supersede the information already incorporated by reference. Any statement contained in this prospectus or a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or a subsequently filed document incorporated by reference modifies or replaces that statement. The SEC file number for the documents incorporated by reference in this prospectus is 001-38670.

The following documents are incorporated by reference into this document:

- [our Annual Report on Form 10-K for the year ended December 31, 2018, filed with the SEC on March 29, 2019;](#)
- [our Definitive Proxy Statement on Schedule 14A, filed with the SEC on April 30, 2019](#) (excluding those portions that are not incorporated by reference into our [Annual Report on Form 10-K for the fiscal year ended December 31, 2018](#));
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2019 and June 30, 2019, filed with the SEC on [May 14, 2019](#) and [August 12, 2019](#), respectively;
- our Current Reports on Form 8-K filed with the SEC on [January 22, 2019](#), [April 30, 2019](#), [June 24, 2019](#) and [August 6, 2019](#), to the extent the information in such reports is filed and not furnished; and
- [the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on September 21, 2018, including any amendments or reports filed for the purposes of updating this description.](#)

We also incorporate by reference into this prospectus all documents (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items) that are filed by us with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (i) after the date of the initial filing of the registration statement of which this prospectus forms a part and prior to effectiveness of the registration statement, or (ii) after the date of this prospectus but prior to the termination of the offering. These documents include periodic reports, such as Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, as well as proxy statements.

Notwithstanding the statements in the preceding paragraphs, no document, report or exhibit (or portion of any of the foregoing) or any other information that we have “furnished” to the SEC pursuant to the Exchange Act shall be incorporated by reference into this prospectus.

We will provide to each person, including any beneficial owner, to whom a prospectus is delivered, without charge upon written or oral request, a copy of any or all of the documents that are incorporated by reference into this prospectus but not delivered with the prospectus, including exhibits that are specifically incorporated by reference into such documents. You should direct any requests for documents to Entasis Therapeutics Holdings Inc., Attn: Elizabeth M. Keiley, General Counsel, 35 Gatehouse Drive, Waltham, Massachusetts 02451; telephone: (781) 810-0120.

\$17,500,000



COMMON STOCK

PROSPECTUS SUPPLEMENT

CANTOR

August 27, 2021
