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Registration No. 333-234041

PROSPECTUS SUPPLEMENT
(To Prospectus dated October 17, 2019)



**\$20,000,000 of Common Stock
plus 104,167 Commitment Shares**

Common Stock

Pursuant to this prospectus supplement and the accompanying prospectus, we are offering up to \$20,000,000 aggregate amount plus 104,167 shares of our common stock, par value \$0.001 per share, or Common Stock, to Aspire Capital Fund, LLC, or Aspire Capital, under a Common Stock Purchase Agreement entered into on October 21, 2019, or the Purchase Agreement.

The shares offered include (i) 104,167 shares of Common Stock to be issued to Aspire Capital Fund, LLC in consideration for entering into the Common Stock Purchase Agreement, or the Commitment Shares, and (ii) additional shares of Common Stock in an aggregate offering price of up to \$20,000,000 which may be sold from time to time to Aspire Capital over the 30-month term of the Purchase Agreement, or the Purchase Shares. The purchase price for the Purchase Shares will be based upon one of two formulas set forth in the Purchase Agreement depending on the type of purchase notice we submit to Aspire Capital from time to time.

Our Common Stock is listed on The Nasdaq Global Market under the symbol "ETTX." On October 18, 2019, the last reported sale price of our Common Stock was \$5.75 per share.

We are an "emerging growth company" as defined by the Jumpstart Our Business Startups Act of 2012 and, as such, we are eligible for reduced public company reporting requirements. Please see "Prospectus Supplement Summary—Implications of Being an Emerging Growth Company."

Our business and an investment in our Common Stock involve significant risks. See "Risk Factors" beginning on page S-7 of this prospectus supplement and page 7 of the accompanying prospectus to read about factors that you should consider before making an investment decision.

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

The date of this prospectus supplement is October 21, 2019

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of the Common Stock we are offering. The second part, the accompanying prospectus dated October 17, 2019, gives more general information about our Common Stock. You should read this prospectus supplement and the accompanying prospectus, including the information incorporated by reference and any free writing prospectuses we have authorized for use in connection with this offering, in their entirety before making an investment decision.

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

Unless the context requires otherwise, the words "Entasis," "we," "the company," "us" and "our" refer to Entasis Therapeutics Holdings Inc. and its subsidiaries taken as a whole.

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

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

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

This prospectus supplement and the accompanying prospectus, including the information incorporated by reference into this prospectus supplement and the accompanying prospectus, include trademarks, service marks and trade names owned by us or others. All trademarks used herein are the property of their respective owners.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and information appearing elsewhere in this prospectus supplement, in the accompanying prospectus and in the documents we incorporate by reference. This summary is not complete and does not contain all of the information that you should consider before making an investment decision. To fully understand this offering and its consequences to you, you should read this entire prospectus supplement and the accompanying prospectus carefully, including the factors described under the heading "Risk Factors" in this prospectus supplement beginning on page S-7 and page 7 of the accompanying prospectus, together with any free writing prospectus we have authorized for use in connection with this offering and the financial statements and all other information incorporated by reference in this prospectus supplement and the accompanying prospectus.

Entasis Therapeutics Holdings Inc.

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 by our nonprofit collaborator, the Global Antibiotic Research and Development Partnership, or GARDP, and was initiated in September 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 NBP are not subject to inactivation by β -lactamases, unlike β -lactam antibiotics. Accordingly, we believe our NBP 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.

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 non-affiliates 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 Offering

Shares of Common Stock offered	Up to \$20,000,000 of shares of Common Stock plus 104,167 Commitment Shares
Common Stock to be outstanding after the offering	Up to 16,716,965 shares, assuming the issuance of 104,167 Commitment Shares and sales of 3,478,260 shares of Common Stock at an assumed price of \$5.75 per share, which was the closing price of our Common Stock on The Nasdaq Global Market on October 18, 2019. The actual number of shares issued will vary depending on the sales prices under this offering.
Manner of offering	Issuance of 104,167 Commitment Shares to Aspire Capital in consideration for entering into the Purchase Agreement and additional Purchase Shares to Aspire Capital from time to time, subject to certain minimum stock price requirements, and daily and other caps, for an aggregate offering price of up to \$20,000,000. See "The Aspire Transaction" and "Plan of Distribution."
Use of proceeds	We currently expect to use the net proceeds from this offering for general corporate purposes, including working capital.
Risk factors	See "Risk Factors" beginning on page S-7 for a discussion of factors you should consider before buying shares of our Common Stock.
Nasdaq Global Market Symbol	"ETTX"

The number of shares of Common Stock to be outstanding after the offering is based on the number of shares outstanding as of June 30, 2019. As of that date, we had 13,134,538 shares of Common Stock outstanding, excluding, as of June 30, 2019:

- 2,096,348 shares issuable upon the exercise of outstanding stock options at a weighted average exercise price of \$6.28 per share; and
- 1,013,316 additional shares reserved for future issuance under our equity incentive plans, including our employee stock purchase plan.

Unless otherwise noted, the information in this prospectus supplement reflects and assumes no exercise of outstanding options subsequent to June 30, 2019.

RISK FACTORS

Investing in our Common Stock involves a high degree of risk. This prospectus supplement does not describe all of those risks. You should consider the risk factors described in this prospectus under the caption "Risks Related to This Offering and Our Common Stock" below, as well as the those described under the caption "Risk Factors" in the documents incorporated by reference herein, including our most recent [Annual Report on Form 10-K](#) and subsequent [Quarterly Reports on Form 10-Q](#) as filed with the Securities and Exchange Commission, or SEC, together with the other information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering, before making an investment decision. 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 Common Stock, and the occurrence of any of these risks might cause you to lose all or part of your investment.

Risks Related to This Offering and Our Common Stock

Sales of our Common Stock to Aspire Capital may cause substantial dilution to our existing stockholders and the sale of the shares of our Common Stock acquired by Aspire Capital could cause the price of our Common Stock to decline.

This prospectus supplement relates to the 104,167 Commitment Shares and the Purchase Shares that we may issue and sell to Aspire Capital from time to time pursuant to the Purchase Agreement. It is anticipated that the Purchase Shares offered to Aspire Capital in this offering will be sold over a period of up to 30 months from the date of this prospectus supplement. The number of shares ultimately offered for sale to Aspire Capital under this prospectus supplement is dependent upon the number of shares we elect to sell to Aspire Capital under the Purchase Agreement. Depending upon market liquidity at the time, sales of shares of our Common Stock under the Purchase Agreement may cause the trading price of our Common Stock to decline.

Aspire Capital may ultimately purchase all, some or none of the shares of Common Stock that, together with the Commitment Shares, is the subject of this prospectus supplement. After Aspire Capital has acquired shares under the Purchase Agreement, it may sell all, some or none of those shares. Sales to Aspire Capital by us pursuant to the Purchase Agreement under this prospectus supplement may result in substantial dilution to the interests of other holders of our Common Stock. The sale of a substantial number of shares of our Common Stock to Aspire Capital in this offering, or anticipation of such sales, could make it more difficult for us to sell equity or equity-related securities in the future at a time and at a price that we might otherwise wish to effect sales. However, we have the right to control the timing and amount of any sales of our shares to Aspire Capital and the Purchase Agreement may be terminated by us at any time at our discretion without any cost to us.

We have a right to sell up to 50,000 Purchase Shares per day under our Purchase Agreement with Aspire Capital, which total may be increased by mutual agreement up to an additional 2,000,000 Purchase Shares per day. The extent to which we rely on Aspire Capital as a source of funding will depend on a number of factors, including the prevailing market price of our Common Stock and the extent to which we are able to secure working capital from other sources. The aggregate number of shares that we can sell to Aspire Capital under the Purchase Agreement may in no case exceed 2,625,594 shares of our Common Stock (which is equal to approximately 19.99% of the Common Stock outstanding on the date of the Purchase Agreement), including the Commitment Shares, or the Exchange Cap, unless stockholder approval is obtained to issue more, in which case the Exchange Cap will not apply.

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Future sales of a significant 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 shares of our Common Stock.

Sales of a substantial number of our shares of Common Stock in the public markets, or the perception that such sales could occur, could depress the market price of our shares of Common Stock and impair our ability to raise capital through the sale of additional equity securities. A substantial number of shares of Common Stock are being offered by this prospectus supplement, and we cannot predict if and when Aspire Capital may sell such shares in the public markets. We cannot predict the number of these shares that might be sold nor the effect that future sales of our shares of Common Stock would have on the market price of our shares of Common Stock.

We will have broad discretion in 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 yield a return.

We will have broad discretion over the use of proceeds from this offering. You may not agree with our decisions, and our use of the proceeds may not yield any return on your investment in us. Our failure to apply the net proceeds of this offering effectively could result in financial losses that could materially impair our ability to pursue our growth strategy, cause the price of our Common Stock to decline, delay development of our product candidates, or require us to raise additional capital.

Terms of subsequent financings may adversely impact our stockholders.

To finance our future business plans and working capital needs, we will have to raise funds through the issuance of equity or debt securities in addition to sales in the Aspire transaction. Depending on the type and the terms of any financing we pursue, stockholders' rights and the value of their investment in our Common Stock could be reduced. A financing could involve one or more types of securities including common stock, convertible debt or warrants to acquire common stock. These securities could be issued at or below the then prevailing market price for our Common Stock. In addition, if we issue secured debt securities, the holders of the debt would have a claim to our assets that would be senior to the rights of stockholders until the debt is paid. Interest on these debt securities would increase costs and negatively impact operating results. If the issuance of new securities results in diminished rights to holders of our Common Stock, the market price of our Common Stock could be negatively impacted.

We do not currently intend to pay dividends on our Common Stock, and any return to investors is expected to come, if at all, only from potential increases in the price of our Common Stock.

At the present time, we intend to use available funds to finance our operations. Accordingly, while payment of dividends rests within the discretion of our board of directors, we have no intention of paying any such dividends in the foreseeable future. Any return to investors is expected to come, if at all, only from potential increases in the price of our Common Stock.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents we have filed with the SEC that are incorporated by reference contain "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Exchange Act. These statements relate to future events or to our future operating or financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements may include, but are not limited to, statements about:

- 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;
- our estimates regarding future expenses, capital requirements and needs for additional financing;
- our intended use of the net proceeds from offerings of our securities under this prospectus supplement and related prospectus; and
- any statement of assumptions underlying any of the foregoing.

In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "potential" and similar expressions intended to identify forward-looking statements. These statements reflect our current views with respect to future events and are based on assumptions and are subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We discuss in greater detail many of these risks under the heading "Risk Factors," in any free writing prospectuses we may authorize for use in connection with this

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offering, and in our most recent [annual report on Form 10-K](#) and in our most recent [quarterly report on Form 10-Q](#), as well as any amendments thereto reflected in subsequent filings with the SEC, which are incorporated by reference into this prospectus supplement and accompanying prospectus in their entirety. Also, these forward-looking statements represent our estimates and assumptions only as of the date of the document containing the applicable statement. Unless required by law, we undertake no obligation to update or revise any forward-looking statements to reflect new information or future events or developments. You should read this prospectus supplement and the accompanying prospectus, together with the documents we have filed with the SEC that are incorporated by reference and any free writing prospectus that we may authorize for use in connection with this offering completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of the forward-looking statements in the foregoing documents by these cautionary statements.

USE OF PROCEEDS

We will retain broad discretion over the use of the net proceeds from this offering. We currently expect to use the net proceeds from this offering for working capital and general corporate purposes. Pending the application of the net proceeds, we expect to invest the proceeds in investment-grade, interest-bearing instruments or other securities.

DILUTION

Our net tangible book value as of June 30, 2019 was \$57.8 million, or \$4.40 per share of Common Stock. Net tangible book value per share is calculated by subtracting our total liabilities from our total tangible assets, which is total assets less intangible assets, and dividing this amount by the number of shares of Common Stock outstanding.

After giving effect to the issuance of the 104,167 Commitment Shares and the sale of additional shares of our Common Stock in the aggregate amount of \$20,000,000 at an assumed offering price of \$5.75 per share, the last reported sale price of our Common Stock on The Nasdaq Global Market on October 18, 2019, and after deducting estimated offering expenses payable by us, our net tangible book value as of June 30, 2019, would have been \$77.7 million, or \$4.65 per share of Common Stock. This represents an immediate increase in the net tangible book value of \$0.25 per share to our existing stockholders and an immediate and substantial dilution in net tangible book value of \$1.10 per share to Aspire Capital. The following table illustrates this per share dilution:

Assumed offering price per share	\$ 5.75
Net tangible book value per share as of June 30, 2019	\$ 4.40
Increase per share attributable to Aspire Capital	0.25
As adjusted net tangible book value per share after this offering	4.65
Net dilution per share to Aspire Capital	<u>\$ 1.10</u>

The above discussion and table are based on 13,134,538 shares of our Common Stock outstanding as of the close of business on June 30, 2019. This number excludes, as of the close of business on June 30, 2019:

- 2,096,348 shares issuable upon the exercise of outstanding stock options at a weighted average exercise price of \$6.28 per share;
- 1,013,316 additional shares reserved for future issuance under our equity incentive plans, including our employee stock purchase plan.

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

THE ASPIRE TRANSACTION

General

On October 21, 2019, we entered into the Purchase Agreement with Aspire Capital, which provides that, upon the terms and subject to the conditions and limitations set forth therein, Aspire Capital is committed to purchase up to an aggregate of \$20,000,000 Purchase Shares from time to time over the 30-month term of the Purchase Agreement. As consideration for entering into the Purchase Agreement, we agreed to issue 104,167 Commitment Shares.

We are filing this prospectus supplement with regard to the offering of our Common Stock consisting of (i) the Commitment Shares and (ii) the Purchase Shares that we may sell to Aspire Capital pursuant to the Purchase Agreement.

Purchase of Shares under the Purchase Agreement

On October 21, 2019, the conditions necessary for purchases under the Purchase Agreement to commence were satisfied. On any business day over the 30-month term of the Purchase Agreement, we have the right, in our sole discretion, to present Aspire Capital with a purchase notice, or a Purchase Notice, directing Aspire Capital to purchase up to 50,000 Purchase Shares per business day, provided that Aspire Capital will not be required to buy Purchase Shares pursuant to a Purchase Notice that was received by Aspire Capital on any business day on which the last closing trade price of our Common Stock on The Nasdaq Global Market (or alternative national exchange in accordance with the Purchase Agreement) is below \$0.25. We and Aspire Capital also may mutually agree to increase the number of shares that may be sold to as much as an additional 2,000,000 Purchase Shares per business day. The purchase price per Purchase Share pursuant to such Purchase Notice, or the Purchase Price, is the lower of:

- (i) the lowest sale price for our Common Stock on the date of sale; or
- (ii) the average of the three lowest closing sale prices for our Common Stock during the 10 consecutive business days ending on the business day immediately preceding the purchase date.

The applicable Purchase Price will be determined prior to delivery of any Purchase Notice.

In addition, on any date on which we submit a Purchase Notice to Aspire Capital for 50,000 Purchase Shares, we also have the right, in our sole discretion, to present Aspire Capital with a volume-weighted average price purchase notice, or a VWAP Purchase Notice, directing Aspire Capital to purchase an amount of our Common Stock equal to up to 30% of the aggregate shares of our Common Stock traded on the next business day, or the VWAP Purchase Date, subject to a maximum number of shares determined by us, or the VWAP Purchase Share Volume Maximum. The purchase price per Purchase Share pursuant to such VWAP Purchase Notice, or the VWAP Purchase Price, shall be the lesser of the closing sale on the VWAP Purchase Date or 97% of the volume weighted average price for our Common Stock traded on (i) the VWAP Purchase Date if the aggregate shares to be purchased on that date does not exceed the VWAP Purchase Share Volume Maximum, or (ii) the portion of such business day until such time as the aggregate shares to be purchased will equal the VWAP Purchase Share Volume Maximum.

The number of Purchase Shares covered by and timing of each Purchase Notice are determined by us, at our sole discretion. The aggregate number of shares that we can sell to Aspire Capital under the Purchase Agreement may in no case exceed the Exchange Cap of 2,626,165 shares of our Common Stock, including the Commitment Shares, unless (i) stockholder approval is obtained to issue more, in which case the Exchange Cap will not apply, or (ii) stockholder approval has not been obtained and at any time the Exchange Cap is reached and at all times thereafter the average price paid for all shares

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issued under the Purchase Agreement (including the Commitment Shares) is equal to or greater than a price equal to \$5.75, which is the closing sale price immediately preceding the execution of the Purchase Agreement; provided that at no time shall Aspire Capital (together with its affiliates) beneficially own more than 19.99% of our Common Stock. Aspire Capital has no right to require any sales by us, but is obligated to make purchases from us as we direct in accordance with the Purchase Agreement. There are no limitations on use of proceeds, financial or business covenants, restrictions on future fundings, rights of first refusal, participation rights, penalties or liquidated damages in the Purchase Agreement. We did not pay any additional amounts to reimburse or otherwise compensate Aspire Capital in connection with the transaction. The Purchase Agreement may be terminated by us at any time, at our discretion, without any penalty or cost to us.

Events of Default

Aspire Capital may terminate the Purchase Agreement upon the occurrence of any of the following events of default:

- the effectiveness of any registration statement that is required to be maintained effective pursuant to the terms of the registration rights agreement between us and Aspire Capital lapses for any reason (including, without limitation, the issuance of a stop order) or is unavailable for sale of shares of our Common Stock in accordance with the terms of the registration rights agreement, and such lapse or unavailability continues for a period of 10 consecutive business days or for more than an aggregate of 30 business days in any 365-day period, which is not in connection with a post-effective amendment to any such registration statement or the filing of a new registration statement; provided, however, that in connection with any post-effective amendment to such registration statement or filing of a new registration statement that is required to be declared effective by the SEC, such lapse or unavailability may continue for a period of no more than 30 consecutive business days, which such period shall be extended for an additional 30 business days if we receive a comment letter from the SEC in connection therewith;
- the suspension from trading or failure of our Common Stock to be listed on our principal market for a period of three consecutive business days;
- the delisting of our Common Stock from our principal market, provided our Common Stock is not immediately thereafter trading on the New York Stock Exchange, the NYSE American, the Nasdaq Global Select Market, the Nasdaq Global Market, or the Nasdaq Capital Market;
- our transfer agent's failure to issue to Aspire Capital shares of our Common Stock which Aspire Capital is entitled to receive under the Purchase Agreement within five business days after an applicable purchase date;
- any breach by us of the representations or warranties or covenants contained in the Purchase Agreement or any related agreements which could have a material adverse effect on us, Aspire Capital or the value of our Common Stock, subject to a cure period of five business days;
- if we become insolvent; and
- any participation or threatened participation in insolvency or bankruptcy proceedings by or against us.

Our Termination Rights

We may terminate the Purchase Agreement at any time, in our discretion, without any cost or penalty.

No Short-Selling or Hedging by Aspire Capital

Aspire Capital has agreed that neither it nor any of its agents, representatives and affiliates shall engage in any direct or indirect short-selling or hedging of our Common Stock during any time prior to the termination of the Purchase Agreement.

Effect of Performance of the Purchase Agreement on Our Stockholders

The Purchase Agreement does not limit the ability of Aspire Capital to sell any or all of the shares it currently owns or receives in this offering. It is anticipated that shares sold to Aspire Capital in this offering will be sold to Aspire Capital over a period of up to 30 months from the date of the Purchase Agreement. The subsequent resale by Aspire Capital of our Common Stock may cause the market price of our Common Stock to decline or to be highly volatile. Aspire Capital may ultimately purchase all, some or none of the shares of Common Stock that, together with the Commitment Shares, is the subject of this prospectus supplement. Aspire Capital may resell all, some or none of the Commitment Shares and any Purchase Shares it acquires. Therefore, sales to Aspire Capital by us pursuant to the Purchase Agreement and this prospectus supplement also may result in substantial dilution to the interests of other holders of our Common Stock. However, we have the right to control the timing and amount of any sales of our shares to Aspire Capital and the Purchase Agreement may be terminated by us at any time at our discretion without any cost to us.

Amount of Potential Proceeds to be Received under the Purchase Agreement

Under the Purchase Agreement, we may sell Purchase Shares having an aggregate offering price of up to \$20,000,000 to Aspire Capital from time to time. The number of shares ultimately offered for sale to Aspire Capital in this offering is dependent upon the number of shares we elect to sell to Aspire Capital under the Purchase Agreement. In addition, Aspire Capital will not be required to buy Purchase Shares pursuant to a Purchase Notice that was received by Aspire Capital on any business day on which the last closing trade price of our Common Stock on The Nasdaq Global Market (or alternative national exchange in accordance with the Purchase Agreement) is below \$0.25. The following table sets forth the amount of proceeds we would receive from Aspire Capital from the sale of shares at varying purchase prices:

Assumed Average Purchase Price	Proceeds from the Sale of Shares to Aspire Capital Under the Purchase Agreement Registered in this Offering	Number of Shares to be Issued in this Offering at the Assumed Average Purchase Price(1)	Percentage of Outstanding Shares After Giving Effect to the Purchased Shares Issued to Aspire Capital(2)
\$ 0.25	\$ 630,500	2,521,998	16.0%
\$ 1.00	\$ 2,521,998	2,521,998	16.0%
\$ 2.50	\$ 6,304,995	2,521,998	16.0%
\$ 5.75	\$ 14,501,489	2,521,998	16.0%
\$ 10.00	\$ 20,000,000	2,000,000	13.1%
\$ 12.00	\$ 20,000,000	1,666,667	11.2%

- (1) Includes the total number of Purchase Shares (but not Commitment Shares) which we would have sold under the Purchase Agreement at the corresponding assumed purchase price set forth in the adjacent column, up to an aggregate purchase price of \$20,000,000, subject to the Exchange Cap.
- (2) The denominator is based on 13,134,538 shares outstanding as of June 30, 2019, plus the (i) 104,167 Commitment Shares issued to Aspire Capital and (ii) number of shares set forth in the adjacent column which we would have sold to Aspire Capital. The numerator is based on the number of shares which we may issue to Aspire Capital under the

Purchase Agreement (that are the subject of this offering) at the corresponding assumed purchase price set forth in the adjacent column.

Information with Respect to Aspire Capital

Aspire Capital Partners LLC, or the Aspire Partners, is the Managing Member of Aspire Capital Fund LLC, or Aspire Fund. SGM Holdings Corp, or SGM, is the Managing Member of Aspire Partners. Mr. Steven G. Martin is the president and sole shareholder of SGM, as well as a principal of Aspire Partners. Mr. Erik J. Brown is the president and sole shareholder of Red Cedar Capital Corp, or Red Cedar, which is a principal of Aspire Partners. Mr. Christos Komissopoulos is president and sole shareholder of Chrisko Investors Inc., or Chrisko, which is a principal of Aspire Partners. Mr. William F. Blank, III is president and sole shareholder of WML Ventures Corp., or WML Ventures, which is a principal of Aspire Partners. Each of Aspire Partners, SGM, Red Cedar, Chrisko, WML Ventures, Mr. Martin, Mr. Brown, Mr. Komissopoulos and Mr. Blank may be deemed to be a beneficial owner of our Common Stock held by Aspire Fund. Each of Aspire Partners, SGM, Red Cedar, Chrisko, WML Ventures, Mr. Martin, Mr. Brown, Mr. Komissopoulos and Mr. Blank disclaims beneficial ownership of our Common Stock held by Aspire Fund.

PLAN OF DISTRIBUTION

Aspire Capital is an "underwriter" within the meaning of the Securities Act.

Neither we nor Aspire Capital can presently estimate the amount of compensation that any agent will receive. We know of no existing arrangements between Aspire Capital, any other stockholder, broker, dealer, underwriter, or agent relating to the sale or distribution of the shares offered by this prospectus supplement. At the time a particular offer of shares is made, a prospectus supplement, if required, will be distributed that will set forth the names of any agents, underwriters, or dealers and any other required information.

We will pay all of the expenses incident to the registration, offering, and sale of the shares to Aspire Capital. We have agreed to indemnify Aspire Capital and certain other persons against certain liabilities in connection with the offering of shares of Common Stock offered hereby, including liabilities arising under the Securities Act or, if such indemnity is unavailable, to contribute amounts required to be paid in respect of such liabilities. Aspire Capital has agreed to indemnify us against liabilities under the Securities Act that may arise from certain written information furnished to us by Aspire Capital specifically for use in this prospectus or, if such indemnity is unavailable, to contribute amounts required to be paid in respect of such liabilities.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to our directors, officers, and controlling persons, we have been advised that in the opinion of the SEC this indemnification is against public policy as expressed in the Securities Act and is therefore, unenforceable.

Aspire Capital and its affiliates have agreed not to engage in any direct or indirect short selling or hedging of our Common Stock during the term of the Purchase Agreement.

We have advised Aspire Capital that it is required to comply with Regulation M promulgated under the Exchange Act. With certain exceptions, Regulation M precludes the selling stockholder, any affiliated purchasers, and any broker-dealer or other person who participates in the distribution from bidding for or purchasing, or attempting to induce any person to bid for or purchase any security which is the subject of the distribution until the entire distribution is complete. Regulation M also prohibits any bids or purchases made in order to stabilize the price of a security in connection with the distribution of that security. All of the foregoing may affect the marketability of the shares offered hereby this prospectus.

We may suspend the sale of shares to Aspire Capital pursuant to this prospectus for certain periods of time for certain reasons, including if the prospectus is required to be supplemented or amended to include additional material information.

This offering will terminate on the date that all shares offered by this prospectus have been sold to Aspire Capital.

LEGAL MATTERS

Cooley LLP, Washington, D.C., will pass upon the validity of the issuance of the securities being sold in this offering.

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.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to "incorporate by reference" information from other documents that we file with it, which means that we can disclose important information to you by referring you to those documents. The information incorporated by reference herein is considered to be part of this prospectus supplement and the accompanying prospectus. Information in this prospectus supplement supersedes information in the accompanying prospectus or incorporated by reference that we filed with the SEC prior to the date of this prospectus supplement, while information that we file later with the SEC will automatically update and supersede the information in this prospectus supplement and the accompanying prospectus. We incorporate by reference into this prospectus supplement, the accompanying prospectus and the registration statement of which this prospectus is a part the information or documents listed below that we have filed with the SEC (Commission File No. 000-38670):

- [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](#), [August 6, 2019](#) and [October 21, 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 supplement 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 after the date of this prospectus supplement 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.

Information in such future filings updates and supplements the information provided in this prospectus supplement and the accompanying prospectus. Any statements in any such future filings will

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automatically be deemed to modify and supersede any information in any document we previously filed with the SEC that is incorporated or deemed to be incorporated herein by reference to the extent that statements in the later filed document modify or replace such earlier statements.

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.

In addition, our annual, quarterly and current reports, proxy statements and other information are filed 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 also maintain a website at www.entasistx.com. Information contained in or accessible through our website does not constitute a part of this prospectus supplement.

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 7 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

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- 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

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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;

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- 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

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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.

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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;

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

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

Conversion or Exchange Rights

We will set forth in the 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;

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

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

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

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

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

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

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

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

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

Modification of Indenture; Waiver

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

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

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

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

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

Discharge

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

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

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

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company, or 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

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

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

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange 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;

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- 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 depository 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 depository on behalf of other financial institutions that participate in the depository'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 depository or its participants. Consequently, for global securities, we will recognize only the depository as the holder of the securities, and we will make all payments on the securities to the depository. The depository 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 depository 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 depository'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 depository 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 depository 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

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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 depository'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 depository. 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 depository. Unless we specify otherwise in the applicable prospectus supplement, the DTC, New York, New York, will be the depository 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 depository, its nominee or a successor depository, 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 depository, 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 depository 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.

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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 depository, as well as general laws relating to securities transfers. We do not recognize an indirect holder as a holder of securities and instead deal only with the depository that holds the global security.

If securities are issued only 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 depository's policies, which may change from time to time, will govern payments, transfers, exchanges and other matters relating to an investor's interest in the global security;
- we and any applicable trustee have no responsibility for any aspect of the depository's actions or for its records of ownership interests in the global security, nor will we or any applicable trustee supervise the depository in any way;
- the depository 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 depository'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.

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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.

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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 overallocation, stabilizing transactions, short covering transactions and penalty bids. Overallocation 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

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- [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.



**\$20,000,000 of Common Stock
plus 104,167 Commitment Shares**

Prospectus Supplement

October 21, 2019
