

PROSPECTUS

**18,691,588 Shares of Common Stock****9,345,794 Warrants to Purchase
Shares of Common Stock****1,161,916 Pre-Funded Warrants to
Purchase Shares of Common Stock**

This prospectus relates to the resale by the selling stockholders named herein, or its pledgees, donees, transferees or other successors in interest, from time to time, of up to (i) 8,183,878 shares of our common stock, \$0.001 par value per share, or the Common Stock, (ii) warrants to purchase 9,345,794 shares of our Common Stock, or the Common Warrants, (iii) pre-funded warrants to purchase 1,161,916 shares of our Common Stock, or the Pre-Funded Warrants (and, together with the Common Warrants, the Warrants), and (iv) 10,507,710 shares of our Common Stock issuable upon exercise of the Warrants, all of which were initially issued pursuant to the Securities Purchase Agreement dated as of August 27, 2020, or the Securities Purchase Agreement, by and between Entasis Therapeutics Holdings Inc. and the selling stockholders. The shares of Common Stock and the Warrants issued pursuant to the Securities Purchase Agreement and the shares of Common Stock issuable upon exercise of the Warrants are referred to herein as the Securities. We are registering the Securities on behalf of the selling stockholders, to be offered and sold from time to time, to satisfy certain registration rights that we have granted to the selling stockholders.

The selling stockholders may resell or dispose of the Securities, or interests therein, at fixed prices, at prevailing market prices at the time of sale or at prices negotiated with purchasers, to or through underwriters, broker-dealers, agents, or through any other means described in the section of this prospectus entitled "Plan of Distribution". The selling stockholders will each bear their respective commissions and discounts, if any, attributable to the sale or disposition of the Securities, or interests therein, held by such selling stockholder. We will bear all costs, expenses and fees in connection with the registration of the Securities. We will not receive any of the proceeds from the sale of the Securities by the selling stockholders.

Our Common Stock is listed on The Nasdaq Global Market, or Nasdaq, under the symbol "ETTX." On October 9, 2020, the last reported sale price of our Common Stock was \$2.02 per share. You are urged to obtain current market quotations for our Common Stock.

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 this prospectus and under similar headings in the other documents that are incorporated by reference into this prospectus as described on page 5 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 13, 2020.

TABLE OF CONTENTS

| | |
|---|--------------------|
| ABOUT THIS PROSPECTUS | i |
| SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS | ii |
| SUMMARY | 1 |
| RISK FACTORS | 5 |
| USE OF PROCEEDS | 6 |
| THE SELLING STOCKHOLDERS | 7 |
| DESCRIPTION OF CAPITAL STOCK | 10 |
| DESCRIPTION OF WARRANTS | 14 |
| PLAN OF DISTRIBUTION | 16 |
| LEGAL MATTERS | 18 |
| EXPERTS | 18 |
| WHERE YOU CAN FIND MORE INFORMATION | 19 |
| INCORPORATION OF CERTAIN INFORMATION BY REFERENCE | 19 |

ABOUT THIS PROSPECTUS

This prospectus provides you with a general description of the Securities that may be resold by the selling stockholders. In certain circumstances, we may provide a prospectus supplement that will contain specific information about the terms of a particular offering by the selling stockholders. We also may provide a prospectus supplement to add information to, or update or change information contained in, this prospectus. To the extent there is a conflict between the information contained in this prospectus and the prospectus supplement, you should rely on the information in the prospectus supplement, provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date — for example, a document incorporated by reference in this prospectus or any prospectus supplement — the statement in the later-dated document modifies or supersedes the earlier statement.

You should read both this prospectus and any applicable prospectus supplement together with the additional information about our company to which we refer you in the sections of this prospectus entitled “Where You Can Find More Information” and “Incorporation of Certain Information by Reference.” You should rely only on the information contained in or incorporated by reference into this prospectus and any prospectus supplement. Neither we nor the selling stockholders have authorized any dealer, sales person or other person to provide you with different information. You should not assume that the information in this prospectus or any prospectus supplement is accurate as of any date other than the date on the front of those documents or that any document incorporated by reference is accurate as of any date other than its filing date. You should not consider this prospectus to be an offer or solicitation relating to the Securities in any jurisdiction in which such an offer or solicitation relating to the Securities is not authorized. Furthermore, you should not consider this prospectus to be an offer or solicitation relating to the Securities if the person making the offer or solicitation is not qualified to do so, or if it is unlawful for you to receive such an offer or solicitation.

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.

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 for the year ended December 31, 2019](#) and our most recent Quarterly Reports 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,” “continue,” “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 Securities Exchange Act of 1934, as amended, or Exchange Act, these forward-looking statements include, but are not limited to, statements regarding:

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

- our estimated needs for, and ability to secure 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.

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 before making an investment decision. For a more complete understanding of our Company, you should read and consider carefully the more detailed information included or incorporated by reference in this prospectus and any applicable prospectus supplement, including the factors described under the heading “Risk Factors” beginning on page 5 of this prospectus, as well as the information incorporated by reference from our most recent Annual Report on Form 10-K and our most recent Quarterly Reports on Form 10-Q, before making an investment decision.

Company Overview

We are an advanced, clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of novel antibacterial products that treat serious infections caused by multidrug-resistant Gram-negative bacteria. Leveraging our targeted-design platform, our strategy is to discover and develop novel molecules that overcome mechanisms of antibiotic resistance in specific bacterial pathogens.

Our lead product candidate, sulbactam-durlobactam, or SUL-DUR, is dosed intravenously, or IV, and is a combination of sulbactam, an IV β -lactam antibiotic, and durlobactam, a novel broad-spectrum intravenous β -lactamase inhibitor, that we are developing for the treatment of multidrug-resistant infections caused by *Acinetobacter baumannii*, or *Acinetobacter*. We initiated ATTACK, our single Phase 3 registration trial in April 2019. As of October 1, 2020, 91 clinical sites across 16 countries are open, including 19 sites in China, and we continue to enroll patients, although some sites in high COVID-19 impact areas have experienced disruptions in new patient enrollment due to redirection of resources as dictated by local conditions. As we continue to actively advance the ATTACK Phase 3 registration trial, we remain in close contact with our contract research organization, or CRO, principal investigators and clinical sites and continue to actively assess the impact of COVID-19 on our expected timeline. However, the timing, scope, and duration of any disruptions in enrollment due to COVID-19 are unpredictable. As a consequence, we are unable to assess the impact of COVID-19 on the timeline for the Phase 3 registration trial and had previously suspended guidance for when we anticipate reporting top-line data from this study. To date, the COVID-19 pandemic has not had a material impact on our supply chain or on our ability to supply SUL-DUR to clinical trial sites. We remain confident that the data from the ATTACK trial, along with data from our other clinical trials of SUL-DUR, will be sufficient to submit an NDA to the FDA.

Our second late-stage product candidate, zoliflodacin, is a novel orally administered molecule being developed for the treatment of uncomplicated gonorrhea. The bacterial pathogen responsible for gonorrhea is *Neisseria gonorrhoeae*, or *N. gonorrhoeae*, including multidrug-resistant strains. We believe there is a growing global unmet patient need for a single-dose oral antibiotic that will reliably treat patients with gonorrhea, including infections caused by multidrug-resistant strains of *N. gonorrhoeae*. The sponsor for the Phase 3 registration trial is our nonprofit collaborator, the Global Antibiotic Research and Development Partnership, or GARDP. The Phase 3 registration trial was initiated in September 2019. Given the focus at our clinical trial sites to address the immediate medical needs of the COVID-19 pandemic, GARDP, with our full agreement, made the decision in late-March to temporarily suspend patient enrollment into the Phase 3 registration trial at U.S. sites and activation of new clinical trial sites in ex-U.S. regions. In July 2020, GARDP resumed patient enrollment at U.S. sites and activation of new clinical trial sites in ex-U.S. regions. However, given the uncertain impact of COVID-19 on our global clinical trial sites, in consultation with GARDP, we are unable to assess the impact of COVID-19 on the timeline for the Phase 3 registration trial, and therefore, had previously suspended guidance for when we anticipate reporting top-line data from the trial. We continue to actively assess the impact of COVID-19 on our expected timeline in consultation with GARDP and will update information as available. To date, the COVID-19 pandemic has not had a material impact on our supply chain or on our ability to supply zoliflodacin to clinical trial sites. We remain confident that the Phase 3 registration trial data, along with data from our other clinical trials of zoliflodacin, will be sufficient for submitting an NDA to the FDA.

We are also developing ETX0282CPDP for the treatment of complicated urinary tract infections, or cUTIs, including those caused by extended-spectrum β -lactamase, producing bacterial strains and carbapenem-resistant *Enterobacteriaceae*, or CRE. ETX0282CPDP is an orally dosed combination of

ETX0282 with cefpodoxime proxetil. We believe there is a significant unmet need for new oral antibiotics to reliably treat the estimated 3 to 4 million patients diagnosed annually with cUTIs. As we reported in June 2019, our preliminary Phase 1 trial results demonstrated that the extended release formulation development achieved the preclinical proof-of-concept of the desired pharmacokinetic profile. We are now progressing with development of an appropriate clinical formulation to be initially evaluated in a future Phase 1 clinical trial before progression to clinical studies in patients. To date, this program has not been materially impacted by the COVID-19 pandemic.

Lastly, we are using our targeted-design platform to develop a novel class of antibiotics, non β -lactam inhibitors of penicillin-binding proteins, or NBPs. 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*. During the fourth quarter of 2019 we selected ETX0462 as a candidate for this program, which we continue to progress through preclinical development. To date, this program has not been materially impacted by the COVID-19 pandemic.

Corporate Information

We were 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. Our corporate website address is www.entasistx.com. Information contained on or accessible through our website is not incorporated by reference into this prospectus, or any accompanying prospectus supplement, and you should not consider such information as part of this prospectus, or any accompanying prospectus supplement, when deciding whether to purchase our securities.

Implications of Being an Emerging Growth 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.

Private Placement

On August 27, 2020, we entered into a securities purchase agreement, or the Securities Purchase Agreement, with the selling stockholders, pursuant to which we issued and sold to the selling stockholders 8,183,878 newly issued shares of our Common Stock and 9,345,794 Common Warrants with an exercise price per share of \$2.675, plus 1,161,916 Pre-Funded Warrants with an exercise price per share of \$0.001, for gross proceeds of \$25.0 million, or the Private Placement. The Warrants are exercisable immediately and have a five year term.

In addition, in connection with the Private Placement and as required by the Securities Purchase Agreement, on September 1, 2020, we entered into a registration rights agreement with the selling stockholders, or the Registration Rights Agreement, in which we agreed to prepare and file with the SEC a registration statement with respect to resales of the Securities purchased by the selling stockholders under the Securities Purchase Agreement. Accordingly, as required by the Registration Rights Agreement, the registration statement of which this prospectus is a part relates to the offer and resale of the Securities issued to the selling stockholders pursuant to the Securities Purchase Agreement.

| The Offering | |
|--|---|
| Issuer | Entasis Therapeutics Holdings Inc. |
| Securities offered by the selling stockholders | 8,183,878 shares of Common Stock. 9,345,794 Common Warrants. 1,161,916 Pre-Funded Warrants. |
| Terms of the Common Warrants | Each Common Warrant entitles the selling stockholders to purchase one share of Common Stock, subject to any adjustments, at an exercise price of \$2.675 per share. The Common Warrants are exercisable immediately and have a five year term. |
| Terms of the Pre-Funded Warrants | Each Pre-Funded Warrant entitles the selling stockholders to purchase one share of Common Stock, subject to any adjustments, at an exercise price of \$0.001 per share. The Pre-Funded Warrants are exercisable immediately and have a five year term. |
| Terms of the offering | The selling stockholders will each determine when and how they will sell the Securities offered in this prospectus, as described in the “Plan of Distribution.” |
| Use of proceeds | We will not receive any proceeds from the sale of the Securities by the selling stockholders in this offering. See “Use of Proceeds.” |
| Risk factors | Investing in our Common Stock involves a high degree of risk. You should carefully read and consider the information beginning on page 5 of this prospectus set forth under the heading “Risk Factors” and all other information set forth in this prospectus and the documents incorporated herein by reference before deciding to invest in our Common Stock. |
| Nasdaq symbol | “ETTX” |

RISK FACTORS

Investing in our securities involves a high degree of risk. Before making an investment decision, you should carefully consider the risks described in the sections entitled “Risk Factors” in our most recent Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q, as filed with the SEC, which are incorporated herein by reference in their entirety, as well any amendment or updates to our risk factors reflected in subsequent filings with the SEC, including any applicable prospectus supplement. For a description of these reports and documents, and information about where you can find them, see “Where You Can Find More Information” and “Incorporation of Certain Information by Reference.” 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.

USE OF PROCEEDS

We will not receive any proceeds from the sale of the Securities covered by this prospectus and any accompanying prospectus supplement. All proceeds from the sale of the Securities will be for the respective accounts of the selling stockholders named herein.

We will bear all other costs, fees and expenses incurred in effecting the registration of the Securities covered by this prospectus and any accompanying prospectus supplement, including, without limitation, all registration and filing fees, Nasdaq listing fees and fees and expenses of our counsel and our accountants, in accordance with the terms of the Registration Rights Agreement. Each selling stockholder will each pay any discounts, commissions, and fees of underwriters, selling brokers, dealer managers or similar securities industry professionals incurred by such selling stockholder in disposing of the Securities covered by this prospectus.

THE SELLING STOCKHOLDERS

We have prepared this prospectus to allow the selling stockholders or their pledgees, donees, transferees or other successors in interest, to sell or otherwise dispose of, from time to time, up to 18,691,588 shares of Common Stock and 10,507,710 Warrants to purchase shares of Common Stock.

On August 27, 2020, we entered into a Securities Purchase Agreement with the selling stockholders, pursuant to which we issued and sold to the selling stockholders an aggregate of 8,183,878 newly issued shares of our Common Stock and 9,345,794 Common Warrants with an exercise price per share of \$2.675, plus 1,161,916 Pre-Funded Warrants with an exercise price per share of \$0.001, for gross proceeds of \$25.0 million. In connection with certain registration rights we granted to the selling stockholders pursuant to the Registration Rights Agreement, we filed with the SEC a registration statement on Form S-3, of which this prospectus forms a part, with respect to the resale or other disposition of the Securities offered by this prospectus from time to time on Nasdaq, in privately negotiated transactions or otherwise. We have agreed to prepare and file amendments and supplements to the registration statement to the extent necessary to keep the registration statement effective for the period of time required under our agreement with the selling stockholders.

The following table sets forth the name of each selling stockholders and the aggregate number of Securities that the selling stockholders may offer and sell pursuant to this prospectus. The selling stockholders may sell some, all or none of the Securities. We do not know how long the selling stockholders will hold the Securities before selling them, and we currently have no agreements, arrangements or understandings with the selling stockholder regarding the sale or other disposition of any of the Securities. The Securities may be offered and sold from time to time by the selling stockholders pursuant to this prospectus. The information below assumes the offer and sale of all Securities beneficially owned by the selling stockholders and available for sale under this prospectus and assumes no further acquisitions or dispositions of Securities by the selling stockholders.

| Name and Address of Selling Stockholder | Before Offering | | After Offering | |
|---|--|--|---|---|
| | Number of Shares of Common Stock Beneficially Owned ⁽¹⁾ | Number of Shares of Common Stock Offered | Number of Shares of Common Stock Beneficially Owned | Percentage of Shares of Common Stock Beneficially Owned |
| Innoviva, Inc. ⁽²⁾ | 37,345,794 ⁽³⁾⁽⁴⁾ | 9,345,794 ⁽³⁾ | 28,000,000 ⁽⁴⁾ | 51.7% ⁽⁷⁾ |
| Armistice Capital Master Fund Ltd. ⁽⁵⁾ | 9,345,794 ⁽⁶⁾ | 9,345,794 ⁽⁶⁾ | — | — |

- (1) “Beneficial ownership” is a term broadly defined by the SEC in Rule 13d-3 under the Exchange Act, and includes more than the typical form of stock ownership, that is, stock held in the person’s name. The term also includes what is referred to as “indirect ownership,” meaning ownership of shares as to which a person has or shares investment power. For purposes of this table, a person or group of persons is deemed to have “beneficial ownership” of any shares that are currently exercisable or exercisable within 60 days of October 1, 2020.
- (2) The principal business address of Innoviva, Inc. is 1350 Old Bayshore Highway, Suite 400, Burlingame, California, 94010.
- (3) Consists of (a) 4,672,897 shares of Common Stock and (b) 4,672,897 Common Warrants.
- (4) Consists of (a) 14,000,000 shares of Common Stock and (b) 14,000,000 shares of Common Stock issuable upon exercise of warrants issued pursuant to a securities purchase agreement, dated as of April 12, 2020.
- (5) The principal business address of Armistice Capital Master Fund Ltd. is c/o Armistice Capital, LLC, 510 Madison Avenue, 7th Floor, New York, NY 10022. Armistice Capital, LLC, the investment manager of Armistice Capital Master Fund Ltd., or Armistice, and Steven Boyd, the managing member of Armistice Capital, LLC, hold shared voting and dispositive power over the shares held by Armistice. Each of Armistice Capital, LLC and Steven Boyd disclaims beneficial ownership of the securities listed except to the extent of their pecuniary interest therein.

- (6) Consists of (a) 3,510,981 shares of Common Stock, (b) 4,672,897 Common Warrants and (c) 1,161,916 Pre-Funded Warrants.
- (7) Based on 35,475,441 shares of Common Stock outstanding as of October 1, 2020, plus (i) warrants to purchase 14,000,000 shares of Common Stock acquired by Innoviva on June 11, 2020 and (ii) 4,672,897 Common Warrants acquired by Innoviva on September 1, 2020.

Relationship with the Selling Stockholders

Securities Purchase Agreement

As discussed above under the section “Summary — Private Placement,” on August 27, 2020, we entered into the Securities Purchase Agreement with the selling stockholders, pursuant to which we issued and sold to the selling stockholders an aggregate of 8,183,878 newly issued shares of our Common Stock and 9,345,794 Common Warrants with an exercise price per share of \$2.675, plus 1,161,916 Pre-Funded Warrants with an exercise price per share of \$0.001, for gross proceeds of \$25.0 million.

As previously disclosed, on April 12, 2020, we entered into a securities purchase agreement with Innoviva, pursuant to which we issued and sold to Innoviva 14,000,000 shares of our Common Stock and 14,000,000 warrants to purchase shares of our Common Stock with an exercise price of \$2.50, for gross proceeds of approximately \$35.0 million.

Registration Rights Agreement

Pursuant to the Registration Rights Agreement with the selling stockholders, we agreed to prepare and file with the SEC the registration statement of which this prospectus forms a part that permits the resale of the Securities and, subject to certain exceptions, use reasonable best efforts to keep such registration statement effective under the Securities Act until (i) all Securities registered by the registration statement have been sold, transferred or otherwise disposed of by the selling stockholders, (ii) the Securities are sold, transferred or otherwise disposed of pursuant to Rule 144 of the Securities Act, or (iii) the Securities have become eligible for sale by the selling stockholders pursuant to Rule 144 without any restriction on the volume or manner of such sale and all restrictive legends and stop transfer instructions have been removed with respect to all book entries representing the Securities.

We have also agreed, among other things, to indemnify the selling stockholders and officers, directors, members, employees and agents, successors and assigns, and any person who controls either of the selling stockholders (within the meaning of the Securities Act or the Exchange Act) from all losses and liabilities arising under the registration statement of which this prospectus forms a part and any securities laws applicable to the registration statement of which this prospectus forms a part and to pay all fees and expenses (including all reasonable costs of preparation and reasonable attorneys’, accountants’ and experts’ fees).

Common Warrants

The Common Warrants are exercisable at any time on or after the date of issuance and entitle the selling stockholders to purchase shares of our Common Stock for a period of five years from the date of issuance at a price per share equal to \$2.675 per share, subject to certain adjustments.

Pre-Funded Warrants

The Pre-Funded Warrants are exercisable at any time on or after the date of issuance and entitle Armistice Capital Master Fund Ltd. to purchase shares of our Common Stock for a period of five years from the date of issuance at a price per share equal to \$0.001 per share.

Investor Rights Agreement

On April 22, 2020 we entered into an investor rights agreement, or the Investor Rights Agreement, with Innoviva. The Investor Rights Agreement provides that for so long as Innoviva and its affiliates hold at least 15% of the outstanding shares of our Common Stock on a fully-diluted basis, Innoviva has the right to designate two directors to our board of directors, or the Board, and for so long as Innoviva and its affiliates hold at least 8% of the outstanding shares of our Common Stock on a fully-diluted basis, Innoviva has the right to designate one director to the Board, subject to certain qualifications and conditions in the Investor Rights Agreement. The Investor Rights Agreement also provides for participation rights for Innoviva in

future offerings of securities by the Company. As of the date hereof, Innoviva has not exercised this right to designate any directors to the Board.

Except as described above, neither the selling stockholder nor any persons having control over such selling stockholder have held any position or office with us or our affiliates within the last three years or has had a material relationship with us or any of our predecessors or affiliates within the past three years, other than as a result of the ownership of our shares of Common Stock or other securities.

DESCRIPTION OF CAPITAL STOCK

The following summary of the material terms of our capital stock is not intended to be a complete summary of the rights and preferences of such securities. We urge to read our amended and restated certificate of incorporation, as amended, and the amended and restated bylaws, which are filed as exhibits to the registration statement of which this prospectus is part, in their entirety for a complete description of the rights and preferences of our capital stock.

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 may establish the rights and preferences of the preferred stock from time to time. As of October 9, 2020, we had outstanding 35,475,441 shares of Common Stock.

Common Stock

Voting Rights

Each holder of our 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 66 $\frac{2}{3}$ % 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 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.

Registration Rights

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

Demand Registration Rights

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

Piggyback Registration Rights

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

S-3 Registration Rights

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

Other Provisions

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

We will pay the registration expenses, other than underwriting discounts, selling commissions and stock transfer taxes, of up to \$50,000 for the shares registered pursuant to the demand, piggyback and Form S-3 registrations described above. The registration rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholder 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 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. The existence of authorized but unissued shares of preferred stock enables our Board 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 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 to fill vacant directorships. In addition, the number of directors constituting our Board may be set only by resolution adopted by a majority vote of our entire Board. These provisions prevent a stockholder from increasing the size of our Board and gaining control of our Board 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, our chief executive officer or president or by our Board pursuant to a resolution adopted by a majority of the total number of authorized directors.
- ***Advance Notice Requirements for Stockholder Proposals and Director Nominations.*** Our amended and restated bylaws provide advance notice requirements for stockholders seeking to bring business before our annual meeting of stockholders, or to nominate candidates for election as directors at our annual meeting of stockholders. Our amended and restated bylaws also specify certain requirements as to the form and content of a stockholder’s notice. These provisions may make it more difficult for our stockholders to bring matters before our annual meeting of stockholders or to nominate directors at annual meetings of stockholders.

We designed these provisions to enhance the likelihood of continued stability in the composition of our Board 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 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 and authorized at an annual or special meeting of the stockholders, and not by written consent, by the affirmative vote of at least 66 $\frac{2}{3}$ % 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. 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. 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.

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 WARRANTS

The following description of our Warrants is a summary. Except as otherwise specified herein, the terms of the Common Warrants and the Pre-Funded Warrants are the same. You should also refer to the forms of warrant certificates, which are filed as exhibits to the registration statement of which this prospectus is part.

Exercisability

The Common Warrants have an exercise price of \$2.675 per share of Common Stock and are exercisable for a period of five years from the date of issuance until 2025. The Pre-Funded Warrants have an exercise price of \$0.001 per share of Common Stock and are exercisable for a period of five years from the date of issuance until 2025. Each Warrant entitles the holder to purchase one share of Common Stock, subject to any adjustments specified in the applicable warrant certificate.

The Warrants may be exercisable by each holder, in whole or in part, by surrendering the applicable warrant certificate and delivering to us a duly completed and executed subscription form, or any other written notice in a form reasonably satisfactory to us, accompanied by the purchase price for the number of shares of Common Stock purchased upon such exercise.

Exercise Limitations

No shares of Common Stock will be issued pursuant to the exercise of any Warrant if the issuance of such shares of Common Stock would violate applicable securities laws.

Adjustments

If we, at any time while the Warrant is outstanding: (i) subdivide or combine our outstanding Common Stock or any other securities exercisable in shares of Common Stock, (ii) make or issue, or fix a record date for the determination of, holders of Common Stock entitled to receive, a dividend or other distribution payable in additional shares of Common Stock or other securities of the Company, cash or other property, (iii) effect a reorganization, recapitalization, reclassification, consolidation, merger or similar transaction, or (iv) enter into a fundamental transaction, as described in the applicable warrant certificate, then, in each case, the exercise price of the Warrant and the number of shares of Common Stock issuable upon exercise of the Warrant will be proportionately adjusted such that the aggregate exercise price or exchange basis will remain unchanged. Further, if we declare or make a distribution or dividend of cash or securities of the Company, then the holder of each Warrant shall be entitled to participate in such distribution.

Transferability

Subject to applicable laws and any reasonable requirements as we may require, the Warrants may be transferred by each holder by surrendering the applicable warrant certificate and delivering to us a duly completed and executed transfer form.

No Listing

There is no established public trading market for the Warrants and we do not expect a market to develop. In addition, we do not intend to apply for listing of the Warrants on any securities exchange or recognized trading system. Without an active market, the liquidity of the Warrants will be limited.

Fundamental Transactions

In the event of any fundamental transaction, as described in the applicable warrant certificate and generally including any merger with or into another entity, a sale, assignment, transfer, conveyance of all or substantially all of our properties or assets, a tender offer or exchange offer, a business combination or change in control, or a reorganization, recapitalization or reclassification of our shares of Common Stock, then upon any subsequent exercise of a Warrant, the holder will have the right to receive as alternative consideration, for each share of our Common Stock that would have been issuable upon such exercise

immediately prior to the occurrence of such fundamental transaction, the number of shares of common stock of the successor entity of our Company, as adjusted in accordance with the applicable warrant certificate.

Cashless Exercise

Unless the Warrants could otherwise be exercised in accordance with the terms of the applicable warrant certificate, then without payment of the aggregate exercise price due on such exercise, the holder may elect instead to receive upon such exercise the number of shares of Common Stock determined according to a formula set forth in the applicable warrant certificate. In the event that a cashless exercise results in a fractional number, we are required to pay cash in equivalent value in lieu of any fractional shares that would be due on exercise.

Rights as a Stockholder

Except as otherwise provided in the applicable warrant certificate or by virtue of a holder's ownership of shares of Common Stock, the holders of the Warrants do not have the rights or privileges of holders of our Common Stock, including any voting rights, until they exercise their Warrants.

Amendments

Amendments and waivers of the terms of the applicable warrant certificate require our written consent and those of the holders of the Warrants.

PLAN OF DISTRIBUTION

The selling stockholders, including their pledgees, donees, transferees, distributees, beneficiaries or other successors in interest, may from time to time offer some or all of the Securities by this prospectus. We will not receive any of the proceeds from the sale of the Securities covered by this prospectus by the selling stockholders. The selling stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. We will bear all fees and expenses incident to our obligation to register the Securities covered by this prospectus.

The selling stockholders may each sell all or a portion of the Securities beneficially owned by it and offered hereby from time to time directly or through one or more underwriters, broker-dealers or agents. If the Securities are sold through underwriters or broker-dealers, the selling stockholders will each be responsible for underwriting discounts or commissions or agent's commissions in connection with the Securities held by such selling stockholders. The Securities may be sold on any national securities exchange or quotation service on which the Securities may be listed or quoted at the time of sale, in the over-the-counter market or in transactions otherwise than on these exchanges or systems or in the over-the-counter market and in one or more transactions at fixed prices, at prevailing market prices at the time of the sale, at varying prices determined at the time of sale, or at privately negotiated prices. These sales may be effected in transactions, which may involve crosses or block transactions.

The selling stockholders may use any one or more of the following methods when disposing of Securities or interests therein:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the Securities as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an over-the-counter distribution;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- short sales effected after the effective date of the registration statement of which this prospectus is a part;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- in "at the market" offerings, as defined in Rule 415 under the Securities Act, at negotiated prices, at prices prevailing at the time of sale or prices related to such prevailing market prices, including sales made directly on a national securities exchange or sales made through a market maker other than on an exchange or other similar offerings through sales agents;
- through trading plans entered into by the selling stockholders pursuant to Rule 10b5-1 under the Exchange Act, that are in place at the time of an offering pursuant to this prospectus and any applicable prospectus supplement hereto that provide for periodic sales of their securities on the basis of parameters described in such trading plans;
- through firm-commitment underwritten public offerings;
- a combination of any such methods of sale; or
- any other method permitted pursuant to applicable law.

The selling stockholders may each, from time to time, pledge or grant a security interest in some or all of the Securities owned by it and, if it defaults in the performance of its secured obligations, the pledgees or secured parties may offer and sell the Securities, from time to time, under this prospectus, or under an amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act amending the list of the selling stockholders to include the pledgee, transferee, or other successors in interest as the selling stockholders under this prospectus. The selling stockholders also may transfer the Securities

in other circumstances, in which case the transferees, pledgees or other successors in interest will be the beneficial owners for purposes of this prospectus.

In connection with the sale of Securities, or interests therein, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the Common Stock in the course of hedging the positions it assumes. The selling stockholders may also sell Securities short and deliver the Securities to close out its short positions, or loan or pledge the Securities to broker-dealers that in turn may sell these securities. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of Securities offered by this prospectus, which Securities such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction).

Broker-dealers engaged by the selling stockholders may arrange for other broker-dealers to participate in sales. If the selling stockholders effects certain transactions by selling Securities to or through underwriters, broker-dealers or agents, such underwriters, broker-dealers or agents may receive commissions in the form of discounts, concessions or commissions from such selling stockholders or commissions from purchasers of the Securities for whom they may act as agent or to whom they may sell as principal. Such commissions will be in amounts to be negotiated, but, except as set forth in a supplement to this prospectus, in the case of an agency transaction will not be in excess of a customary brokerage commission in compliance with applicable rules of the Financial Industry Regulatory Authority, or FINRA; and in the case of a principal transaction a markup or markdown in compliance with applicable FINRA rules.

The aggregate proceeds to the selling stockholders from the sale of the Securities offered by it will be the purchase price of the Securities less discounts or commissions, if any. The selling stockholders reserve the right to accept and, together with their respective agents from time to time, to reject, in whole or in part, any proposed purchase of Securities to be made directly or through agents. The selling stockholders also may resell all or a portion of the Securities in open market transactions in reliance upon Rule 144 under the Securities Act, rather than under this prospectus, provided that it meets the criteria and conforms to the requirements of that rule.

The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of the Securities, or interests therein, may be deemed to be “underwriters” within the meaning of Section 2(a)(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the Securities may be underwriting discounts and commissions under the Securities Act. The selling stockholders are subject to the prospectus delivery requirements of the Securities Act.

To the extent required pursuant to Rule 424(b) under the Securities Act, the Securities to be sold, the names of the selling stockholders, the purchase price and public offering price, the names of any agents, dealer or underwriter, and any applicable commissions or discounts with respect to a particular offer will be set forth in an accompanying prospectus supplement or, if appropriate, a post-effective amendment to the registration statement that includes this prospectus.

In order to comply with the securities laws of some states, if applicable, the Securities may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the Securities may not be sold unless it has been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

The selling stockholders and any other person participating in a sale of the Securities registered under this prospectus will be subject to applicable provisions of the Exchange Act, and the rules and regulations thereunder, including, without limitation, to the extent applicable, Regulation M of the Exchange Act, which may limit the timing of purchases and sales of any of the Securities by the selling stockholders and any other participating person. All of the foregoing may affect the marketability of the Securities and the ability of any person or entity to engage in market-making activities with respect to the Securities. In addition, we will make copies of this prospectus (as it may be supplemented or amended from time to time) available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the Securities against certain liabilities, including liabilities arising under the Securities Act.

LEGAL MATTERS

The validity of the securities offered by this prospectus, and any supplement thereto, will be passed upon by Covington & Burling LLP.

EXPERTS

The consolidated financial statements of Entasis Therapeutics Holdings Inc. as of December 31, 2019 and 2018, 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. The audit report covering the December 31, 2019 consolidated financial statements contains an explanatory paragraph that states that the Company's recurring losses and negative cash flows from operations raise substantial doubt about the entity's ability to continue as a going concern. The consolidated financial statements do not include any adjustments that might result from the outcome of that uncertainty.

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 the selling stockholders is 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. The selling stockholders 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, and is not incorporated into, 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 following documents are incorporated by reference into this document:

- [our Annual Report on Form 10-K for the year ended December 31, 2019, filed with the SEC on March 11, 2020](#);
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2020 and June 30, 2020, filed with the SEC on [May 7, 2020](#) and on [August 6, 2020](#);
- our Current Reports on Form 8-K filed with the SEC on [January 13, 2020](#), [April 13, 2020](#), [April 22, 2020](#), [April 29, 2020](#), [May 21, 2020](#), [June 11, 2020](#), [June 11, 2020](#), [August 19, 2020](#) and [September 1, 2020](#); and
- [the description of our Common Stock contained in Exhibit 4.3 to our Annual Report on Form 10-K for the year ended December 31, 2019, filed with the SEC on March 11, 2020, including any amendments or reports filed for the purposes of updating this description.](#)

All documents subsequently filed by us pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, prior to the filing of a post-effective amendment which indicates that all securities offered hereby have been sold or which deregisters all securities then remaining unsold, shall be deemed to be incorporated by reference into this registration statement and to be a part hereof from the date of filing such documents, except as to specific sections of such documents as set forth therein.

Unless expressly incorporated into this registration statement, a report furnished on Form 8-K (or any portion thereof so furnished) prior or subsequent to the date hereof shall not be incorporated by reference into this registration statement. Any statement contained in a document incorporated or deemed to be incorporated by reference herein shall be deemed to be modified or superseded for purposes of this registration statement to the extent that a statement herein or in any subsequently filed document which also is or is

deemed to be incorporated by reference herein modifies or supersedes such statement. Any such statement so modified or superseded shall not constitute a part of this registration statement, except as so modified or superseded.

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.

**18,691,588 Shares
of Common Stock**

**9,345,794 Warrants to Purchase
Shares of Common Stock**

**1,161,916 Pre-Funded Warrants to Purchase
Shares of Common Stock**



Prospectus

October 13, 2020
