

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

FORM S-3

REGISTRATION STATEMENT

UNDER

THE SECURITIES ACT OF 1933

ENTASIS THERAPEUTICS HOLDINGS INC.

(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

82-4592913
(I.R.S. Employer
Identification Number)

35 Gatehouse Drive
Waltham, Massachusetts 02451
(781) 810-0120

(Address, including zip code, and telephone number, including area code of registrant's principal executive offices)

Manoussos Perros, Ph.D.
Chief Executive Officer
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35 Gatehouse Drive
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(781) 810-0120

(Name, address, including zip code, and telephone number, including area code, of agent for service)

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From time to time after the effective date of this registration statement
(Approximate date of commencement of proposed sale to the public)

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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

Large accelerated filer
Non-accelerated filer

Accelerated filer
Smaller reporting company
Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Amount to be Registered ⁽¹⁾	Proposed Maximum Offering Price per Unit ⁽²⁾	Proposed Maximum Aggregate Offering Price ⁽²⁾	Amount of Registration Fee
Common Stock, par value \$0.001 per share	20,000,000	\$2.35	\$47,043,000.00	\$5,132.40
Warrants to Purchase Common Stock ⁽³⁾	10,000,000	—	—	—

(1) The Registrant is hereby registering for resale from time to time by the selling stockholder named herein of up to (i) 10,000,000 shares of common stock, (ii) 10,000,000 warrants to purchase shares of common stock and (iii) 10,000,000 shares of common stock issuable upon exercise of such warrants, all of which were issued pursuant to the Securities Purchase Agreement, dated as of May 3, 2021, by and between the Registrant and the selling stockholder. Pursuant to Rule 416(a) under the Securities Act of 1933, as amended, or the Securities Act, this registration statement also covers such additional number of shares of common stock that may be issued as a result of stock splits, stock dividends or similar transactions.

(2) Estimated solely for purposes of determining the registration fee pursuant to Rule 457(c) under the Securities Act. The proposed maximum offering price per share and proposed maximum aggregate offering price shown are based on the average of the high and low sale prices of the Registrant's common stock on July 28, 2021 as reported on The Nasdaq Global Market

(3) Pursuant to Rule 457(g) under the Securities Act, no separate registration fee is required for the warrants because the warrants are being registered in the same registration statement as the common stock issuable upon exercise of the warrants.

The Registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment that specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act or until the registration statement shall become effective on such date as the Securities and Exchange Commission, acting pursuant to said Section 8(a), may determine.

SUBJECT TO COMPLETION, DATED AUGUST 2, 2021

PROSPECTUS

**20,000,000 Shares of Common Stock****10,000,000 Warrants to Purchase Shares of Common Stock**

This prospectus relates to the resale by the selling stockholder named herein, or its pledgees, donees, transferees or other successors in interest, from time to time, of up to (i) 10,000,000 shares of our common stock, par value \$0.001 per share, or the Common Stock, (ii) warrants to purchase 10,000,000 shares of our Common Stock, or the Warrants, and (iii) 10,000,000 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 May 3, 2021, or the Securities Purchase Agreement, by and between Entasis Therapeutics Holdings Inc. and the selling stockholder. 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 resale of the Securities on behalf of the selling stockholder, to be offered and sold from time to time, to satisfy certain registration rights that we have granted to the selling stockholder.

The selling stockholder 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 stockholder will bear the commissions and discounts, if any, attributable to the sale or disposition of the Securities, or interests therein, held by the 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 stockholder.

Our Common Stock is listed on The Nasdaq Global Market, or Nasdaq, under the symbol "ETTX." On July 30, 2021, the last reported sale price of our Common Stock was \$2.27 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 _____, 2021.

The information contained in this prospectus is not complete and may be changed. The selling stockholder named in this prospectus may not sell these securities until the registration statement becomes effective. This prospectus is not an offer to sell these securities, and the selling stockholder named in this prospectus is not soliciting offers to buy these securities in any jurisdiction where the offer for sale is not permitted.

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ABOUT THIS PROSPECTUS

This prospectus provides you with a general description of the Securities that may be resold by the selling stockholder. In certain circumstances, we may provide a prospectus supplement that will contain specific information about the terms of a particular offering by the selling stockholder. 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 any 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 stockholder has 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 within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements other than statements of historical fact are “forward-looking statements” for purposes of this prospectus. In some cases, you can identify forward-looking statements by terminology such as “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would” or the negative or plural of those terms, and similar expressions. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other “forward-looking” information.

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

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

The foregoing factors should not be construed as exhaustive and should be read together with the other cautionary statements included in this document. Factors that may cause actual results to differ materially from current expectations include, among other things, those set forth in Part I, Item 1A, “Risk Factors,” in our most recent Annual Report on Form 10-K and those set forth in Part II, Item 1A, “Risk Factors” in our most recent Quarterly Report on Form 10-Q and in any supplement to this prospectus. Any forward-looking statement in this prospectus reflects our current view with respect to future events and is subject to these and other risks, uncertainties and assumptions relating to our operations, results of operations, industry and future growth. Given these uncertainties, you should not rely on these forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, 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 4 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 Report on Form 10-Q, before making an investment decision.

Company Overview

We are an advanced, clinical-stage biopharmaceutical company focused on the discovery, development and commercialization of targeted antibacterial products that address high unmet medical needs to treat serious infections caused by multidrug-resistant pathogens.

Our lead product candidate, sulbactam-durlobactam, or SUL-DUR, is an intravenous combination of sulbactam, a β -lactam antibiotic, and durlobactam, a novel broad-spectrum β -lactamase inhibitor that we are developing for the treatment of pneumonia and bloodstream infections caused by carbapenem-resistant *Acinetobacter baumannii*, or *Acinetobacter*. Based on current carbapenem resistance rates, we estimate there are in excess of 200,000 hospital-treated carbapenem-resistant *Acinetobacter* infections annually across the United States, Europe, the Middle East and China for which significant morbidity and mortality exists due to limited treatment options. We initiated ATTACK (*Acinetobacter* Treatment Trial Against Colistin), our single Phase 3 registration trial in 2019, with top-line data readout expected in the second half of 2021. ATTACK is a global, multi-center trial that will evaluate approximately 120 patients with confirmed carbapenem-resistant *Acinetobacter* hospital-acquired pneumonia, ventilator-acquired pneumonia, ventilated pneumonia or bloodstream infections, or a combination of these. We believe that the data from the ATTACK trial, data from our other clinical trials of SUL-DUR and non-clinical data 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. Intramuscular injections of ceftriaxone now represent the only U.S. Centers for Disease Control and Prevention, or CDC, recommended treatment option for the estimated 1.6 million annual cases of gonorrhea in the United States. We believe there is a growing unmet need for a single-dose oral antibiotic that will reliably treat patients with gonorrhea, including infections caused by multidrug-resistant strains of *N. gonorrhoeae*, which are emerging globally. The Phase 3 registration trial, initiated in September 2019, is a multi-center, open-label, noninferiority trial in approximately 1,000 enrolled patients with uncomplicated gonorrhea. Our nonprofit collaborator, the Global Antibiotic Research and Development Partnership, is the sponsor of the registration trial and is responsible for all trial expenses. We believe data from the Phase 3 registration trial, along with data from our other clinical trials of zoliflodacin and non-clinical data 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 multidrug-resistant *Enterobacteriaceae*. ETX0282CPDP is an oral combination of ETX0282 with cefpodoxime proxetil. We believe there is a significant unmet need for new oral antibiotics to reliably treat the estimated 3 to 4 million patients diagnosed annually with cUTIs. We have reported preliminary Phase 1 trial results, and subsequently demonstrated that an extended release tablet formulation achieved preclinical proof-of-concept of the desired pharmacokinetic profile both *in vitro* and in non-human primates. Having successfully completed the initial Phase 1 studies and preclinical work to deliver a formulation with the desired extended release profile, we are currently prioritizing our resources on completing the ATTACK trial and supporting the ongoing Phase 3 registration trial for zoliflodacin, while we evaluate options for further clinical development of ETX0282CPDP.

Lastly, we are advancing development of a novel class of antibiotics, non β -lactam inhibitors of penicillin-binding proteins, or NBPs. We believe NBPs constitute a potential new class of Gram-negative

antibacterial agents that are designed to target a broad spectrum of multidrug resistant bacterial pathogens that overcome the main source of β -lactam resistance which is driven by β -lactamase activity. This novel class of agent is designed to target a broad spectrum of multidrug resistant bacterial pathogens that are part of the CDC/World Health Organization list of high unmet medical need or ESKAPE pathogens. We selected ETX0462 as the initial clinical candidate for this program, based on demonstrated activity against *Pseudomonas* and a number of high-priority biothreat pathogens combined with a strong preclinical safety profile and attractive physiochemical properties. We currently anticipate completing the required pre-clinical activities by early 2022 to enable the program to advance into a Phase 1 clinical trial. In June 2020, we were awarded a contract from the National Institute of Health, or NIH, to support research towards developing additional NBP molecules with expanded Gram-negative spectrum from this novel class. This research program, designated NBP2, is attempting to target *Klebsiella*, *Pseudomonas* and *E. coli* from the ESKAPE list of pathogens. The NIH contract consists of an initial award of approximately \$3.0 million, with the potential to increase up to \$15.5 million. Subject to achieving pre-defined milestones, the contract is expected to sufficiently fund activities to achieve submission of an Investigational New Drug application to the FDA.

Going Concern

Since our inception, we have incurred recurring net losses and negative cash flows from our operations. We have financed our operations primarily with proceeds from the sale of redeemable convertible preferred stock and the sale of our common stock. As of June 30, 2021, we had cash and cash equivalents of \$56.4 million.

Based on our available cash resources, management expects that our existing cash and cash equivalents as of June 30, 2021 will be sufficient to enable us to fund our operating expenses and capital expenditure requirements through the second quarter of 2022. However, management has concluded that substantial doubt exists about our ability to continue as a going concern for one year from the date that we file our interim financial statements as of and for the period ended June 30, 2021. A failure to raise additional funding or to effectively implement cost reductions could harm our business, results of operations and future prospects. We expect to seek additional funding to sustain our future operations and while we have successfully raised capital in the past, the ability to raise capital in future periods is not assured. If we are not able to secure adequate additional funding in future periods, we may make reductions in certain expenditures. This may include suspending or curtailing planned activities. We may also have to delay, reduce the scope of, suspend or eliminate one or more research and development programs or our commercialization efforts.

Corporate Information

We were incorporated under the laws of the State of Delaware in March 2018. Our shares are listed on Nasdaq, 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 May 3, 2021, we entered into a securities purchase agreement, or the Securities Purchase Agreement, with the selling stockholder, pursuant to which we issued and sold to the selling stockholder 10,000,000 shares of our Common Stock and 10,000,000 Warrants with an exercise price per share of \$2.00, for gross proceeds of \$20 million, or the Private Placement. The Warrants are exercisable immediately and have a five-year term. Pursuant to the Securities Purchase Agreement we issued 3,731,025 shares of our Common Stock and 3,731,025 Warrants on May 3, 2021 and 6,268,975 shares of our Common Stock and 6,268,975 Warrants on June 11, 2021. Our stockholders approved the issuance of greater than 20% of our outstanding shares of Common Stock in the Private Placement at a special meeting of stockholders held on June 10, 2021.

In addition, in connection with the Private Placement and as required by the Securities Purchase Agreement, on May 3, 2021, we entered into a registration rights agreement with the selling stockholder, 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 stockholder 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 stockholder pursuant to the Securities Purchase Agreement.

The Offering

Issuer	Entasis Therapeutics Holdings Inc.
Securities offered by the selling stockholder	20,000,000 shares of Common Stock. 10,000,000 Warrants.
Terms of the Warrants	Each Warrant entitles the selling stockholder to purchase one share of Common Stock, subject to any adjustments, at an exercise price of \$2.00 per share. The Warrants are exercisable immediately and have a five-year term.
Terms of the offering	The selling stockholder will 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 stockholder 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 4 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 our subsequent Quarterly Report 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 account of the selling stockholder 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. The selling stockholder will pay any discounts, commissions, and fees of underwriters, selling brokers, dealer managers or similar securities industry professionals incurred by the selling stockholder in disposing of the Securities covered by this prospectus.

THE SELLING STOCKHOLDER

We have prepared this prospectus to allow the selling stockholder or its pledgees, donees, transferees or other successors in interest, to sell or otherwise dispose of, from time to time, up to 20,000,000 shares of Common Stock and 10,000,000 Warrants to purchase shares of Common Stock.

On May 3, 2021, we entered into a Securities Purchase Agreement with the selling stockholder, pursuant to which we issued and sold to the selling stockholder an aggregate of 10,000,000 shares of our Common Stock and 10,000,000 Warrants with an exercise price per share of \$2.00, for gross proceeds of \$20 million. In connection with certain registration rights we granted to the selling stockholder 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 stockholder.

The following table sets forth the name of the selling stockholder and the aggregate number of Securities that the selling stockholder may offer and sell pursuant to this prospectus. The selling stockholder may sell some, all or none of the Securities. We do not know how long the selling stockholder 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 stockholder pursuant to this prospectus. The information below assumes the offer and sale of all Securities beneficially owned by the selling stockholder and available for sale under this prospectus and assumes no further acquisitions or dispositions of Securities by the selling stockholder.

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 Strategic Opportunities LLC ⁽²⁾	20,000,000 ⁽³⁾	20,000,000 ⁽³⁾	—	—

- (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 August 2, 2021.
- (2) The selling stockholder is a wholly owned subsidiary of Innoviva. The principal business address of Innoviva and the selling stockholder is 1350 Old Bayshore Highway, Suite 400, Burlingame, California, 94010. Innoviva holds 18,672,897 shares of our Common Stock and warrants to purchase an additional 18,672,897 shares of our Common Stock. The securities held by Innoviva have been registered for resale previously on our Registration Statement on Form S-3 (File No. 333-241683) that became effective on August 14, 2020 and our Registration Statement on Form S-3 (File No 333-249315) that became effective on October 13, 2020.
- (3) Consists of (a) 10,000,000 shares of Common Stock and (b) 10,000,000 shares of Common Stock issuable upon exercise of warrants issued pursuant to a securities purchase agreement, dated as of May 3, 2021.

Relationship with the Selling Stockholder

Securities Purchase Agreement

As discussed above under the section “Summary — Private Placement,” on May 3, 2021, we entered into the Securities Purchase Agreement with the selling stockholder, pursuant to which we issued and sold

to the selling stockholder an aggregate of 10,000,000 newly issued shares of our Common Stock and 10,000,000 Warrants with an exercise price per share of \$2.00, for aggregate gross proceeds of \$20 million. Pursuant to the Securities Purchase Agreement we issued 3,731,025 shares of our Common Stock and 3,731,025 Warrants on May 3, 2021 and 6,268,975 shares of our Common Stock and 6,268,975 Warrants on June 11, 2021. Our stockholders approved the issuance of greater than 20% of our outstanding shares of Common Stock in the Private Placement at a special meeting of stockholders held on June 10, 2021.

Registration Rights Agreement

Pursuant to the Registration Rights Agreement with the selling stockholder, 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 stockholder, (ii) the Securities are sold, transferred or otherwise disposed of pursuant to Rule 144 of the Securities Act, (iii) the Securities cease to be outstanding or (iv) the Securities have become eligible for sale by the selling stockholder 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 stockholder, its partners, stockholders, equity holders, general partners, managers, members and affiliates and each of their respective officers and directors, and any person who controls the selling stockholder (within the meaning of the Securities Act or the Exchange Act) and any employee or representative thereof from and against any and 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).

Warrants

The Warrants are exercisable at any time on or after the date of issuance and entitle the selling stockholder 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 \$2.00 per share, subject to certain adjustments.

Investor Rights Agreement

On April 22, 2020 we entered into 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 COMMON STOCK

The following summary of the material terms of our common 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 June 30, 2021, we had outstanding 47,310,254 shares of 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 and selling commissions, for the shares registered pursuant to the demand, piggyback and Form S-3 registrations described above. Reasonable fees and expenses, however, for one counsel to the selling stockholder, shall be capped at \$50,000. 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 chairperson 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. 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 Warrants have an exercise price of \$2.00 per share of Common Stock and are exercisable for a period of five years from the date of issuance until 2026. 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.

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 stockholder, including its 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 stockholder. The selling stockholder 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 stockholder may 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 stockholder will be responsible for underwriting discounts or commissions or agent's commissions in connection with the Securities held by the selling stockholder. 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 stockholder 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 stockholder 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 stockholder 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 stockholder to include the pledgee, transferee, or other successors in interest as the selling stockholder under this prospectus. The selling stockholder 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 stockholder 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 stockholder 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 such securities. The selling stockholder 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 stockholder may arrange for other broker-dealers to participate in sales. If the selling stockholder 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 stockholder 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 stockholder 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 stockholder reserves the right to accept and, together with its 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 stockholder 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 stockholder 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 stockholder is 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 stockholder, 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 they have been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

The selling stockholder 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 stockholder 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 stockholder for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholder 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, 2020 and 2019, and for the years then ended, have been incorporated by reference herein in reliance upon the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

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 stockholder 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 stockholder is 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, 2020, filed with the SEC on [March 23, 2021](#), as subsequently amended on [April 30, 2021](#);
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2020, filed with the SEC on [May 5, 2020](#);
- our Current Reports on Form 8-K filed with the SEC on [May 3, 2021](#) and [June 11, 2021](#); and
- the description of our Common Stock contained in [Exhibit 4.3 to our Annual Report on Form 10-K for the year ended December 31, 2019](#), filed with the SEC on March 11, 2020, including any amendments or reports filed for the purposes of updating this description.

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.

PART II
INFORMATION NOT REQUIRED IN THE PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution.

Set forth below is an estimate (except for registration fees, which are actual) of the approximate amount of the types of fees and expenses listed below that were paid or are payable by us in connection with the issuance and distribution of the Securities to be registered by this registration statement. None of the expenses listed below are to be borne by the selling stockholder named in the prospectus that forms a part of this registration statement.

Expense	Amount
SEC Registration Fee	\$ 5,132.40
Accounting Fees and Expenses	\$ 10,000
Legal Fees and Expenses	\$ 25,000
Miscellaneous	\$ —
Total	\$40,132.40

Item 15. Indemnification of Officers and Directors.

Under Section 145 of the Delaware General Corporation Law, or DGCL, we have broad powers to indemnify our directors and officers against liabilities they may incur in such capacities, including liabilities under the Securities Act. Section 145 of the DGCL generally provides that a Delaware corporation has the power to indemnify its present and former directors, officers, employees and agents against expenses incurred by them in connection with any suit to which they are or are threatened to be made, a party by reason of their serving in such positions so long as they acted in good faith and in a manner they reasonably believed to be in or not opposed to, the best interests of the corporation and, with respect to any criminal action, they had no reasonable cause to believe their conduct was unlawful.

Our amended and restated certificate of incorporation, as amended, and amended and restated bylaws provide that we will limit the liability of our directors, and may indemnify our directors and officers, to the maximum extent permitted by the DGCL. The DGCL provides that directors of a corporation will not be personally liable for monetary damages for breach of their fiduciary duties as directors, except for liability for any:

- breach of their duty of loyalty to the corporation or its stockholders;
- act or omission not in good faith or that involves intentional misconduct or a knowing violation of law;
- unlawful payment of dividends or redemption of shares; or
- transaction from which the directors derived an improper personal benefit.

These limitations of liability do not apply to liabilities arising under federal securities laws and do not affect the availability of equitable remedies such as injunctive relief or rescission.

We entered into separate indemnification agreements with our directors and officers in addition to the indemnification provided for in our amended and restated bylaws. These indemnification agreements provide, among other things, that we will indemnify our directors and officers for certain expenses, including damages, judgments, fines, penalties, settlements and costs and attorneys' fees and disbursements, incurred by a director or officer in any claim, action or proceeding arising in his or her capacity as a director or officer of our company or in connection with service at our request for another corporation or entity. The indemnification agreements also provide for procedures that will apply in the event that a director or officer makes a claim for indemnification.

We also maintain a directors' and officers' insurance policy pursuant to which our directors and officers are insured against liability for actions taken in their capacities as directors and officers. We believe that these indemnification provisions and insurance are useful to attract and retain qualified directors and officers.

Item 16. Exhibits.

Exhibit Number	Description of Document
3.1	Amended and Restated Certificate of Incorporation of the Company (incorporated herein by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on September 28, 2018).
3.1.1	Certificate of Amendment to the Amended and Restated Certificate of Incorporation of the Company (incorporated herein by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on June 11, 2020).
3.2	Amended and Restated Bylaws of the Company (incorporated herein by reference to Exhibit 3.2 to the Company's Current Report on Form 8-K (File No. 001-38670), filed with the SEC on September 28, 2018).
4.1	Form of Common Stock Certificate of the Company (incorporated herein by reference to Exhibit 4.1 to the Company's Registration Statement on Form S-1 (File No. 333-226920), filed with the SEC on August 17, 2018).
4.2	Form of Warrant Certificate (incorporated herein by reference to Exhibit 4.1 to the Company's Current Report on Form 8-K, filed with the SEC on May 3, 2021).
4.3	Registration Rights Agreement, dated May 3, 2021, by and between the Company and the Holder named therein (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K, filed with the SEC on May 3, 2021).
5.1*	Opinion of Covington & Burling LLP.
10.1	Securities Purchase Agreement, dated May 3, 2021, by and between the Company and the Purchaser named therein (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, filed with the SEC on May 3, 2021).
10.2	Investor Rights Agreement, dated April 22, 2020, by and between the Company and Innoviva (incorporated herein by reference to Exhibit 10.1 to the Company's Current Report on Form 8-K, filed with the SEC on April 22, 2020).
23.1*	Consent of KPMG LLP, independent registered public accounting firm.
23.2*	Consent of Covington & Burling LLP (included in Exhibit 5.1).
24.1*	Power of Attorney (included on signature page).

* Filed herewith.

Item 17. Undertakings.

The undersigned registrant hereby undertakes:

- (1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:
 - (i) To include any prospectus required by Section 10(a)(3) of the Securities Act;
 - (ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the SEC pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

- (iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that the undertakings set forth in paragraphs (1)(i), (1)(ii) and (1)(iii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the SEC by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are incorporated by reference in this registration statement or are contained in a form of prospectus filed pursuant to Rule 424(b) that is part of this registration statement.

- (2) That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.
- (3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.
- (4) That, for the purpose of determining liability under the Securities Act to any purchaser:
 - (i) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and
 - (ii) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof. *Provided, however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.
- (5) That, for the purpose of determining liability of the registrant under the Securities Act to any purchaser in the initial distribution of the securities, the undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:
 - (i) any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;
 - (ii) any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;
 - (iii) the portion of any other free writing prospectus relating to the offering containing material information about the undersigned registrant or its securities provided by or on behalf of the

undersigned registrant; and (iv) any other communication that is an offer in the offering made by the undersigned registrant to the purchaser.

- (6) That, for purposes of determining any liability under the Securities Act, each filing of the registrant's annual report pursuant to Section 13(a) or 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the SEC such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

SIGNATURES

Pursuant to the requirements of the Securities Act, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Waltham, Commonwealth of Massachusetts, on August 2, 2021.

ENTASIS THERAPEUTICS HOLDINGS INC.

By: /s/ MANOUSSOS PERROS

Manoussos Perros, Ph.D.
President and Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Manoussos Perros, Ph.D., Michael Gutch, Ph.D. and Elizabeth M. Keiley, and each of them, as his or her true and lawful attorneys-in-fact and agents, each with the full power of substitution and resubstitution, for him or her and in his or her name, place or stead, in any and all capacities, to sign any and all amendments and supplements to this registration statement (including post-effective amendments), and to sign any registration statement for the same offering covered by this registration statement that is to be effective upon filing pursuant to Rule 462(b) promulgated under the Securities Act of 1933, as amended, and all post-effective amendments thereto, and to file the same, with exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary or desirable to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or their or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ MANOUSSOS PERROS Manoussos Perros, Ph.D.	President, Chief Executive Officer and Director (Principal Executive Officer)	August 2, 2021
/s/ MICHAEL GUTCH Michael Gutch, Ph.D.	Chief Business Officer and Chief Financial Officer (Principal Financial Officer and Principal Accounting Officer)	August 2, 2021
/s/ DAVID MEEK David Meek	Chairman of the Board of Directors	August 2, 2021
/s/ HEATHER BEHANNA Heather Behanna, Ph.D.	Director	August 2, 2021
/s/ DAVID C. HASTINGS David C. Hastings	Director	August 2, 2021
/s/ HOWARD MAYER Howard Mayer, M.D.	Director	August 2, 2021
/s/ HEATHER PRESTON Heather Preston, M.D.	Director	August 2, 2021

COVINGTON

BEIJING BRUSSELS DUBAI FRANKFURT JOHANNESBURG
LONDON LOS ANGELES NEW YORK PALO ALTO
SAN FRANCISCO SEOUL SHANGHAI WASHINGTON

Covington & Burling LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956
T +1 202 662 6000

August 2, 2021

Entasis Therapeutics Holdings Inc.
35 Gatehouse Drive
Waltham, MA 02451

Ladies and Gentlemen:

We have acted as counsel to Entasis Therapeutics Holdings Inc., a Delaware corporation (the “Company”), in connection with the registration by the Company under the Securities Act of 1933 (the “Act”), of (i) 10,000,000 shares (the “Issued Shares”) of the Company’s common stock, par value \$0.001 per share (the “Common Stock”), (ii) warrants to purchase 10,000,000 shares of Common Stock (the “Warrants”) and (iii) 10,000,000 shares of Common Stock issuable upon exercise of the Warrants (the “Warrant Shares,” and together with the Issued Shares, the “Shares”), in each case pursuant to the Company’s Registration Statement on Form S-3 (the “Registration Statement”) filed with the Securities and Exchange Commission on the date hereof. The Issued Shares and the Warrants were issued in two tranches on May 3, 2021 and June 11, 2021.

We have reviewed such corporate records, certificates and other documents, and such questions of law, as we have considered necessary or appropriate for the purposes of this opinion. We have assumed that all signatures are genuine, that all documents submitted to us as originals are authentic and that all copies of documents submitted to us conform to the originals.

We have further assumed that the Warrant Shares, if issued in certificated form, will conform to the specimen incorporated by reference as an exhibit to the Registration Statement and will be duly countersigned by the transfer agent of the Company’s Common Stock and duly registered by the registrar of the Company’s Common Stock.

We have relied as to certain matters on information obtained from public officials, officers of the Company and other sources believed by us to be responsible.

Based upon the foregoing, and subject to the qualifications set forth below, we are of the opinion that:

- (1) The Issued Shares have been duly authorized and validly issued and are fully paid and non-assessable.
 - (2) The Warrant Shares initially issuable upon exercise of the Warrants have been duly authorized and reserved for issuance and, when issued and paid for upon exercise in accordance with the terms of the Warrants, will be validly issued, fully paid and non-assessable.
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Entasis Therapeutics Holdings Inc.

August 2, 2021

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(3) The Warrants constitute the valid and binding obligation of the Company, enforceable against the Company in accordance with their terms, subject to bankruptcy, insolvency, fraudulent transfer, reorganization, moratorium and other laws of general applicability relating to or affecting creditors' rights and to general equity principles.

We express no opinion as to: (i) waivers of defenses, subrogation and related rights, rights to trial by jury, rights to object to venue, or other rights or benefits bestowed by operation of law; (ii) releases or waivers of unmatured claims or rights; (iii) indemnification, contribution, exculpation, or arbitration provisions, or provisions for the non-survival of representations, to the extent they purport to indemnify any party against, or release or limit any party's liability for, its own breach or failure to comply with statutory obligations, or to the extent such provisions are contrary to public policy; or (iv) provisions for liquidated damages and penalties, penalty interest and interest on interest.

We are members of the bar of the State of New York and the District of Columbia. We do not express any opinion herein on any laws other than the laws of the State of New York and the Delaware General Corporation Law and reported judicial decisions interpreting these laws.

We hereby consent to the filing of this opinion as Exhibit 5.1 to the Registration Statement. We also hereby consent to the reference to our firm under the heading "Legal Matters" in the prospectus constituting part of the Registration Statement. In giving such consent, we do not thereby admit that we are in the category of persons whose consent is required under Section 7 of the Act.

Very truly yours,

/s/ Covington & Burling LLP

Consent of Independent Registered Public Accounting Firm

We consent to the use of our report dated March 23, 2021, with respect to the consolidated financial statements of Entasis Therapeutics Holdings Inc. incorporated herein by reference and to the reference to our firm under the heading “Experts” in the prospectus.

/s/ KPMG LLP

Boston, Massachusetts

August 2, 2021
