

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and we are not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

Subject to completion, dated November 9, 2021

**PRELIMINARY PROSPECTUS SUPPLEMENT**  
To the Prospectus dated October 1, 2021



## Shares of Common Stock

We are offering \_\_\_\_\_ shares of our common stock, par value \$0.0001 per share, pursuant to this prospectus supplement and the accompanying prospectus.

Our common stock is listed on the Nasdaq Capital Market under the symbol "ATXI." On November [ ], 2021 the last reported sale price of our common stock on the Nasdaq Capital Market was \$[ ] per share.

Investing in our common stock involves a high degree of risk. See "Risk Factors" beginning on page S-6 of this prospectus supplement and page 3 of the accompanying prospectus as well as the information under the caption "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2020 and in our Quarterly Report on Form 10-Q for the quarter ended June 30, 2021, and in the other documents incorporated by reference into this prospectus supplement and the accompanying prospectus for a discussion of the factors you should carefully consider before investing in our common stock.

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

	Per share	Total
Public offering price	\$	\$
Underwriting discounts and commissions <sup>(1)</sup>	\$	\$
Proceeds, before expenses, to us	\$	\$

(1) See "Underwriting" beginning on page S-16 of this prospectus supplement for additional information regarding underwriting compensation.

Delivery of the shares will take place on or about November [ ], 2021. We have granted the underwriters an option for a period of 45 days to purchase an additional \_\_\_\_\_ shares of our common stock. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be \$ \_\_\_\_\_, and the total proceeds to us, before expenses will be \$ \_\_\_\_\_.

## AEGIS CAPITAL CORP.

The date of this prospectus supplement is November [ ], 2021.

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### ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this offering of common stock and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference in this prospectus supplement and the accompanying prospectus. The second part, the accompanying prospectus dated October 1, 2021, including the documents incorporated by reference, provides more general information, some of which may not apply to this offering. Generally, when we refer to this prospectus supplement, we are referring to both parts of this document combined.

To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference that was filed with the U.S. Securities and Exchange Commission (the “SEC”) prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that, if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

We have not, and the underwriters have not, authorized anyone to provide you with information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. When you make a decision about whether to invest in our common stock, you should not rely upon any information other than the information in this prospectus supplement or the accompanying prospectus, including any free writing prospectus that we have authorized for use in this offering. Neither the delivery of this prospectus supplement or the accompanying prospectus, including any free writing prospectus that we have authorized for use in this offering, nor the sale of our common stock means that information contained in this prospectus supplement and the accompanying prospectus, including any free writing prospectus that we have authorized for use in this offering, is correct after their respective dates. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the information incorporated by reference into this prospectus supplement and the accompanying prospectus, and any free writing prospectus that we have authorized for use in connection with this offering in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled “Where You Can Find More Information” and “Incorporation of Certain Information By Reference” in this prospectus supplement.

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

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

Unless otherwise stated, all references in this prospectus supplement to “we,” “us,” “our,” “Avenue,” the “Company” and similar designations refer to Avenue Therapeutics, Inc. This prospectus supplement contains trademarks and trade names of Avenue Therapeutics, Inc., including our name and logo. Other service marks, trademarks and trade names referred to in this document are the property of their respective owners.

**SPECIAL CAUTIONARY NOTICE REGARDING FORWARD-LOOKING STATEMENTS**

This prospectus supplement includes statements that are, or may be deemed, "forward-looking statements." In some cases, these forward-looking statements can be identified by the use of forward-looking terminology, including the terms "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately" or, in each case, their negative or other variations thereon or comparable terminology, although not all forward-looking statements contain these words. They appear in a number of places throughout this prospectus supplement and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our history of net operating losses and uncertainty regarding our ability to obtain regulatory approval from the FDA for our product candidate, our ability to obtain capital and achieve profitability, our ability to develop and commercialize our product candidate, our ability to obtain, perform under and maintain financing and strategic agreements and relationships, our ability to comply with ongoing regulatory requirements, our ability to successfully operate in a competitive industry and gain market acceptance by physician, provider, patient, and payor communities, our reliance on third parties, unstable economic or market conditions, our ability to adapt with the COVID-19 outbreak and its potential impact on our employees' and consultants' ability to complete work in a timely manner and our ability to obtain and adequately protect intellectual property rights for our product candidate.

Some of the factors that we believe could cause actual results to differ from those anticipated or predicted include:

- expectations for increases or decreases in expenses;
- expectations for the clinical and pre-clinical development, manufacturing, regulatory approval, and commercialization of our pharmaceutical product candidate or any other products we may acquire or in-license;
- our use of clinical research centers and other contractors;
- expectations for generating revenue or becoming profitable on a sustained basis;
- expectations or ability to enter into product acquisition and in-licensing transactions;
- expectations or ability to build our own commercial infrastructure to manufacture, market and sell our product candidate;
- acceptance of our product candidate by doctors, patients or payors;
- our plans to develop and commercialize our product candidate;
- our ability to compete against other companies and research institutions;
- the loss of key scientific or management personnel;
- our ability to secure adequate protection for our intellectual property;
- our ability to successfully compete in the potential markets for our product candidate;
- regulatory developments in the United States and foreign countries;
- availability of reimbursement for our product candidate;

- estimates of the sufficiency of our existing cash and cash equivalents to finance our operating requirements;
- market conditions in the pharmaceutical and biotechnology sectors;
- our available cash and cash equivalents;
- the accuracy of our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;
- our ability to obtain additional funding;
- our ability to maintain license agreements for our licensed product candidate;
- the ongoing impact of the COVID-19 pandemic; and
- our ability to successfully implement our strategy.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics, and healthcare, regulatory and scientific developments and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus supplement, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this prospectus supplement. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this prospectus supplement, they may not be predictive of results or developments in future periods. The forward-looking statements contained in this prospectus supplement reflect our views and assumptions only as of the date of this prospectus. Except as required by law, we assume no responsibility for updating any forward-looking statements. We qualify all of our forward-looking statements by these cautionary statements. In addition, with respect to all of our forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

## PROSPECTUS SUPPLEMENT SUMMARY

*This summary highlights certain information about us, this offering and information appearing elsewhere in this prospectus supplement, in the accompanying prospectus and in the documents we incorporate by reference. This summary is not complete and does not contain all of the information that you should consider before making an investment decision. To fully understand this offering and its consequences to you, you should read this entire prospectus supplement and the accompanying prospectus carefully, including the factors described under the heading "Risk Factors" in this prospectus supplement beginning on page S-6 and page 3 of the accompanying prospectus, together with any free writing prospectus we have authorized for use in connection with this offering and the financial statements and all other information incorporated by reference in this prospectus supplement and the accompanying prospectus.*

### CORPORATE SUMMARY

We are a specialty pharmaceutical company that seeks to develop and commercialize our product principally for use in the acute/intensive care hospital setting. Our current product candidate is intravenous ("IV") Tramadol, for the treatment of post-operative acute pain. Under the terms of certain agreements described herein, we have an exclusive license to develop and commercialize IV Tramadol in the United States. In 2016, we completed a pharmacokinetic study for IV Tramadol in healthy volunteers as well as an end of phase 2 meeting with the U.S. Food and Drug Administration ("FDA"). In the third quarter of 2017, we initiated a Phase 3 development program of IV Tramadol for the management of post-operative pain. In December 2019, we submitted a New Drug Application ("NDA") for IV Tramadol and received a Complete Response Letter (the "First CRL") from the FDA in October 2020. In February 2021, we resubmitted the NDA for IV Tramadol. The FDA assigned a Prescription Drug User Fee Act ("PDUFA") goal date of April 12, 2021 for the resubmitted NDA for IV Tramadol. On June 14, 2021, we announced that we had received a second Complete Response Letter (the "Second CRL") from the FDA regarding our NDA for IV tramadol. We continue to pursue regulatory approval for IV Tramadol and had a Type A meeting with the FDA in July 2021. We submitted a formal dispute resolution request ("FDRR") with the Office of Neuroscience of the FDA on July 27, 2021. On August 26, 2021, we received an Appeal Denied Letter from the Office of Neuroscience of the FDA in response to the FDRR submitted on July 27, 2021. On August 31, 2021, we submitted a FDRR with the Office of New Drugs ("OND") of the FDA. On October 21, 2021, we received a written response from the OND of the FDA stating that the OND needs additional input from an Advisory Committee in order to reach a decision on the FDRR. To date, we have not received approval, and there are no assurances that we will receive approval, for the sale of our product candidate in any market and, therefore, have not generated any sales revenue from our product candidate.

### CORPORATE INFORMATION

**Our principal executive offices are located at 1140 Avenue of the Americas, Floor 9, New York, New York 10036, and our telephone number is 781-652-4500. We maintain a website on the Internet at [www.avenuetx.com](http://www.avenuetx.com) and our e-mail address is [info@avenuetx.com](mailto:info@avenuetx.com). Our Internet website, and the information contained on it, are not to be considered part of this prospectus supplement.**

We are a majority-controlled subsidiary of Fortress Biotech, Inc. ("Fortress").

### The Offering

<b>Common stock offered by us</b>	shares of our common stock, par value \$0.0001 per share.
<b>Common stock to be outstanding after the offering</b>	Shares.
<b>Option to purchase additional shares</b>	We have granted the underwriters an option for a period of up to 45 days from the date of this prospectus supplement to purchase up to an aggregate of additional shares of our common stock at the price set forth on the cover page of this prospectus supplement.
<b>Use of Proceeds</b>	<p>The net proceeds from this offering will be used for general corporate purposes and working capital requirements, which may include, among other things, the advancement of our product candidate to obtain regulatory approval from the FDA. We have not determined the amounts we plan to spend on the areas listed above or the timing of these expenditures, and we have no current plans with respect to acquisitions as of the date of this prospectus supplement. As a result, we will have broad discretion to allocate the net proceeds of this offering.</p> <p>See "Use of Proceeds" on page S-11 of this prospectus supplement.</p>
<b>Risk factors</b>	See "Risk Factors" beginning on page S-6, on page 3 of the accompanying prospectus and our "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2020, which is incorporated by reference herein, for a discussion of factors that you should consider before investing in our common stock.
<b>Nasdaq Capital Market symbol</b>	ATXI

The number of shares of common stock to be outstanding after this offering is based on 16,748,068 shares of our common stock outstanding as of June 30, 2021, and excludes:

- 15,576 shares of common stock issuable upon exercise of outstanding warrants having a weighted-average exercise price of \$0.64 per share;
- 1,139,910 shares of common stock issuable upon the vesting and settlement of outstanding restricted stock award/units; and
- 229,436 shares of common stock reserved for issuance and available for future grant under our 2015 Incentive Plan.

## RISK FACTORS

*Investing in our common stock involves a high degree of risk. This prospectus supplement does not describe all of those risks. You should consider the risk factors described in this prospectus supplement under the caption "Risks associated with this offering" below, as well as the those described under the caption "Risk Factors" in the accompanying prospectus, and in the documents incorporated by reference herein, including our Annual Report on Form 10-K for the fiscal year ended December 31, 2020, and in our most recent Quarterly Report on Form 10-Q, together with the other information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus, and in any free writing prospectus that we have authorized for use in connection with this offering, before making an investment decision.*

*If any of these risks occur, our business, financial condition, results of operations and future prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock would likely decline and you may lose all or part of your investment. Share information set forth in these risk factors is as of the dates set forth herein or therein and unless otherwise indicated, does not give effect to the issuance of the securities in connection with this offering.*

### **Risks associated with this offering**

***An active trading market for our common stock may not develop or be sustained and investors may not be able to resell their shares at or above the price at which they purchased them.***

An active trading market for our shares may never develop or be sustained. In the absence of an active trading market for our common stock, investors may not be able to sell their common stock at or above the price they paid or at the time that they would like to sell. In addition, an inactive market may impair our ability to raise capital by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration, which, in turn, could harm our business.

***The trading price of the shares of our common stock has been and is likely to continue to be highly volatile, and purchasers of our common stock could incur substantial losses.***

Our stock price has been and will likely continue to be volatile for the foreseeable future. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their common stock at or above the price they paid.

In addition, in the past, stockholders have initiated class action lawsuits against biotechnology and pharmaceutical companies following periods of volatility in the market prices of these companies'. Such litigation and any litigation that may be instituted against us, our officers and/or our directors in the future, could cause us to incur substantial costs and divert management's attention and resources, which could have a material adverse effect on our business, financial condition and results of operations.

### ***You will experience immediate and substantial dilution.***

Because the price per share of our common stock being offered is substantially higher than the net tangible book value per share of our common stock, you will suffer substantial dilution in the net tangible book value of the common stock you purchase in this offering. If you purchase shares of common stock in this offering, you will suffer immediate and substantial dilution of \$ [ ] per share in the net tangible book value of the common stock. In addition, we may issue additional securities in the future, including shares of common stock, securities that are convertible into or exchangeable for, or that represent the right to receive, common stock or substantially similar securities. The issuance of these securities may cause further dilution to our stockholders. The exercise of outstanding stock options and the vesting of outstanding restricted stock units may also result in further dilution of your investment. See the section entitled "Dilution" below for a more detailed discussion of the dilution you would incur if you purchase securities in this offering.

### ***A substantial number of shares of our common stock could be sold into the public market in the near future, which could depress our stock price.***

Sales of substantial amounts of our common stock in the public market could reduce the prevailing market prices for our common stock. Substantially all of our outstanding common stock are eligible for sale as are common stock issuable under vested and exercisable stock options. If our existing stockholders sell a large number of shares of our common stock, or the public market perceives that existing stockholders might sell shares of common stock, the market price of our common stock could decline significantly. These sales might also make it more difficult for us to sell equity securities at a time and price that we deem appropriate.

### ***We will require additional financing to achieve our goals, and a failure to obtain this capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.***

Since our inception, most of our resources have been dedicated to the discovery, acquisition and preclinical and clinical development of our product candidates. We have expended and believe that we will continue to expend substantial resources for the development of our drug candidate and potential regulatory approval of our drug candidate and may expend additional resources on other product candidates and drug discovery and acquisition efforts. These expenditures will include costs associated with general administration, facilities, research and development, acquiring new technologies, manufacturing product candidates, conducting preclinical experiments and clinical trials, applying for regulatory approvals, commercializing any products that might receive approval for sale, and costs associated with operating as a public company.

We have no significant current source of income to sustain our present activities, and we do not expect to generate income until, and unless, we obtain approval from the FDA or other regulatory authorities, and we successfully commercialize our product candidates. We will need further funding to continue our pursuit of regulatory approval of our product candidate. In addition, other unanticipated costs may arise.

### ***There is substantial doubt about our ability to continue as a going concern, even after completion of this offering, which may hinder our ability to obtain future financing.***

Our unaudited interim condensed financial statements as of June 30, 2021 have been prepared under the assumption that we will continue as a going concern for the next twelve months. As of June 30, 2021, we had cash and cash equivalents of \$1.1 million and an accumulated deficit of \$75.2 million. We do not believe that our cash and cash equivalents are sufficient for the next twelve months. As a result of our financial condition and other factors described herein, there is substantial doubt about our ability to

continue as a going concern. Our ability to continue as a going concern will depend on our ability to obtain additional funding, as to which no assurances can be given. We continue to analyze various alternatives, including amending existing lines of credit, debt or equity financings or other arrangements. Our future success depends on our ability to raise capital and/or implement the various strategic alternatives discussed above. We cannot be certain that these initiatives or raising additional capital, whether through selling additional debt or equity securities or obtaining a line of credit or other loan, will be available to us or, if available, will be on terms acceptable to us. If we issue additional securities to raise funds, these securities may have rights, preferences, or privileges senior to those of our common stock, and our current shareholders may experience dilution. If we are unable to obtain funds when needed or on acceptable terms, we may be required to curtail our current development programs, cut operating costs, forego future development and other opportunities or even terminate our operations.

***Our business and operations could be adversely affected by the effects of health epidemics, including the ongoing COVID-19 pandemic.***

Any potential future clinical trials may experience delays in patient enrollment, potentially due to prioritization of hospital resources toward the COVID-19 pandemic, or concerns among patients about participating in clinical trials during a public health emergency. The COVID-19 pandemic is affecting the operations of government entities, such as the FDA, as well as contract research organizations, third-party manufacturers, and other third-parties upon whom we rely. As a result of “shelter-in-place” orders, quarantines or similar orders or restrictions to control the spread of COVID-19, many companies, including our own, have implemented work-from-home policies for their employees. The effects of these stay at home orders and work-from-home policies may be negatively impacting productivity, resulting in delays in our timelines. The extent of the impact on our operations depends in part on the time these restrictions remain in place, and whether restrictions are reinstated as a result of a rising surge in COVID-19 cases. These and similar disruptions in our operations could negatively impact our business, operating results and financial condition.

The spread of COVID-19 has also led to disruption and volatility in the global capital markets, which increases the cost of, and adversely impacts access to, capital and increases economic uncertainty. To the extent the COVID-19 pandemic adversely affects our business, financial results and value of our common stock, it may also affect our ability to access capital and obtain financing, which could in the future negatively affect our liquidity.

The global pandemic of COVID-19 continues to evolve rapidly, and the ultimate impact of the COVID-19 pandemic or a similar health epidemic is highly uncertain and subject to change. We do not yet know the full impact of potential delays or effects on our business, our ability to access the capital markets, or supply chains or on the global economy as a whole. However, these effects could have a material impact on our operations, and we will continue to monitor the COVID-19 situation closely.

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***We have broad discretion over the use of our cash and cash equivalents, including the net proceeds we receive in this offering, and may not use them effectively.***

Our management has broad discretion to use our cash and cash equivalents including the net proceeds we receive in this offering, to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use to fund operations, we may invest our cash, cash equivalents and marketable securities in a manner that does not produce income or that loses value.

***If we fail to satisfy applicable listing standards, including compliance with the minimum market value of listed securities requirement, our common stock may be delisted from the NASDAQ Capital Market.***

On September 2, 2021, we received a letter from the Listing Qualifications Department of the NASDAQ Stock Market notifying us that, based upon its review for the last 30 consecutive business days, we did not meet the continuing listing requirements of NASDAQ Marketplace Rule 5550(b)(2), which requires that we maintain a minimum market value of listed securities of at least \$35 million. NASDAQ also informed us that we did not meet the requirements of Listing Rules 5550(b)(1) and 5550(b)(3). The notification from the NASDAQ Stock Market does not have an immediate effect on the listing of our common stock and our common stock will continue to trade on the NASDAQ under the symbol “ATXI”. Under NASDAQ’s Listing Rules, we have 180 calendar days from the date of the notification to regain compliance, which will expire on March 1, 2022. If, at any time during this period, the market value of our common stock closes at \$35 million or more for a minimum of 10 consecutive business days, we will regain compliance with this requirement. If we are unable to regain compliance during the 180-day period, we will receive an additional notification that our securities are subject to delisting. We could, at that time, request a hearing to remain on the NASDAQ Capital Market, which request will ordinarily suspend such delisting determination until a decision is made by NASDAQ subsequent to the hearing.

There can be no assurances, however, that we will be successful in regaining compliance with the continued listing requirements and maintaining the listing of our common stock on the NASDAQ Capital Market. Delisting from the NASDAQ could adversely affect our ability to raise additional financing through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common stock. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities. If our common stock is delisted by the NASDAQ the price of our common stock may decline and our common stock may be eligible to trade on the OTC Bulletin Board, another over-the-counter quotation system, or on the pink sheets where an investor may find it more difficult to dispose of their common stock or obtain accurate quotations as to the market value of our common stock. Further, if we are delisted, we would incur additional costs under requirements of state “blue sky” laws in connection with any sales of our securities. These requirements could severely limit the market liquidity of our common stock and the ability of our stockholders to sell our common stock in the secondary market.

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## CAPITALIZATION

The following table sets forth our capitalization as of June 30, 2021:

- on an actual basis; and
- on an as adjusted basis to reflect the sale of the [ ] shares of common stock offered by us in this offering (assuming no exercise of the underwriters’ option to purchase additional shares) after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this table together with our financial statements and related notes and the “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2020 and our Quarterly Report on Form 10-Q for the quarter ended June 30, 2021.

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**June 30, 2021**  
**(unaudited)**

(\$ in thousands, except share and per share amounts)

	<u>Actual</u>	<u>As Adjusted</u>
Cash and cash equivalents	\$ 1,121	\$ 3,866
<b>Stockholders' Equity</b>		
<b>Preferred Stock (\$0.0001 par value), 2,000,000 shares authorized</b>		
Class A Preferred Stock	—	—
<b>Common Stock (\$0.0001 par value), 50,000,000 shares authorized</b>		
Common shares	2	2
Additional paid-in capital	75,855	78,600
Accumulated deficit	(75,215)	(75,215)
Total Stockholders' Equity	642	3,387
<b>Total Capitalization</b>	<b>\$ 1,121</b>	<b>\$ 3,866</b>

The number of shares of common stock to be outstanding after this offering is based on 16,748,068 shares of our common stock outstanding as of June 30, 2021, and excludes:

- 15,576 shares of common stock issuable upon exercise of outstanding warrants having a weighted-average exercise price of \$0.64 per share;
- 1,139,910 shares of common stock issuable upon the vesting and settlement of outstanding restricted stock awards/units; and
- 229,436 shares of common stock reserved for issuance and available for future grant under our 2015 Incentive Plan.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise of the outstanding options or warrants or settlement of outstanding restricted stock units, described above.

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## DILUTION

Purchasers of the shares offered by this prospectus supplement and the accompanying prospectus will suffer immediate and substantial dilution in the net tangible book value per share of the common stock they purchase. Net tangible book value per share represents the amount of total tangible assets less total liabilities, divided by the number of shares of our common stock outstanding as of June 30, 2021. Our net tangible book value as of June 30, 2021 was approximately \$0.6million, or \$0.04per share of our common stock.

Dilution in net tangible book value per share represents the difference between the amount per share paid by purchasers in this offering and the net tangible book value per share of our common stock immediately after this offering. After giving effect to the sale of shares of our common stock in this offering at a public price of \$ per share, and after deducting the underwriting discount and the estimated expenses payable by us, our net tangible book value as of June 30, 2021 would have been approximately \$ million, or \$ per share of common stock. This represents an immediate increase in net book value of \$ per share to our existing stockholders and an immediate dilution in net tangible book value of \$ per share to new investors participating in this offering.

The following table illustrates this calculation on a per share basis:

Offering price per share		\$
Net tangible book value per share as of June 30, 2021	\$	
Increase per share attributable to the offering	\$	
As-adjusted net tangible book value per share after giving effect to the offering		\$
Dilution in net tangible book value per share to new investors		\$

The number of shares of common stock to be outstanding after this offering is based on 16,748,068 shares of our common stock outstanding as of June 30, 2021, and excludes:

- 15,576 shares of common stock issuable upon exercise of outstanding warrants having a weighted-average exercise price of \$0.64 per share;
- 1,139,910 shares of common stock issuable upon the vesting and settlement of outstanding restricted stock awards/units; and
- 229,436 shares of common stock reserved for issuance and available for future grant under our 2015 Incentive Plan.

Unless otherwise indicated, all information in this prospectus supplement assumes no exercise of the outstanding options or warrants or settlement of outstanding restricted stock units, described above.

If the underwriters exercise in full their option to purchase additional shares of our common stock, the as adjusted net tangible book value after this offering would be \$ per share, representing an increase in net tangible book value of \$ per share to existing stockholders and immediate dilution in net tangible book value of \$ per share to purchasers in this offering.

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## USE OF PROCEEDS

We estimate that the proceeds from this offering, after deducting estimated offering expenses payable by us and underwriting fees, will be approximately \$2.7 million.

The net proceeds from this offering will be used for general corporate purposes and working capital requirements, which may include, among other things, the advancement of our product candidate to obtain regulatory approval from the FDA. We have not determined the amounts we plan to spend on the areas listed above or the timing of these expenditures, and we have no current plans with respect to acquisitions as of the date of this prospectus supplement. As a result, we will have broad discretion to allocate the net proceeds of this offering.

The timing and amounts of our actual expenditures will depend on several factors. As of the date of this prospectus supplement, we cannot specify with certainty all of

#### DIVIDEND POLICY

We have never declared or paid any cash dividends or distributions on our capital stock. We currently intend to retain future earnings, if any, to support operations and to finance expansion and therefore we do not anticipate paying any cash dividends on our common stock in the foreseeable future.

#### MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO NON-U.S. HOLDERS

The following is a summary of the material United States federal income tax consequences relating to the acquisition, ownership and disposition of our common stock as of the date hereof. Except where noted, this summary deals only with our common stock that is held as a capital asset (within the meaning of Section 1221 of the Internal Revenue Code of 1986, as amended (the "Code") by a "non-U.S. holder" (as defined below).

For purposes of this summary, a "non-U.S. holder" means a beneficial owner of our common stock (other than a partnership or any other entity treated as a partnership for United States federal income tax purposes) that is not for United States federal income tax purposes any of the following:

- an individual citizen or resident of the United States;
- a corporation (or any other entity treated as a corporation for United States federal income tax purposes) created or organized in or under the laws of the United States, any state thereof or the District of Columbia;
- an estate the income of which is subject to United States federal income taxation regardless of its source; or
- a trust if it (1) is subject to the primary supervision of a court within the United States and one or more United States persons have the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable United States Treasury regulations ("Treasury Regulations") to be treated as a United States person.

You are not a non-U.S. holder if you are a nonresident alien individual present in the United States for 183 days or more in the taxable year of disposition, or if you are a former citizen or former resident of the United States for United States federal income tax purposes. If you are such a person, you should consult your tax adviser regarding the United States federal income tax consequences of the ownership and disposition of our common stock.

This summary is based upon provisions of the Code and Treasury Regulations, administrative rulings and judicial decisions currently in effect, all as of the date hereof and all subject to change at any time, possibly with retroactive effect, or to different interpretation by the Internal Revenue Service ("IRS"). This summary does not address all aspects of United States federal taxes, including the Medicare contribution tax, and does not address any foreign, state, local or other tax considerations that may be relevant to non-U.S. holders in light of their personal circumstances. In addition, this summary does not represent a detailed description of the United States federal income tax consequences applicable to non-U.S. holders that are subject to special treatment under the United States federal income tax laws (including a non-U.S. holder that is a United States expatriate or "controlled foreign corporation"). We cannot provide assurance that a change in law will not alter significantly the tax considerations that we describe in this summary.

If a partnership (or other entity treated as a partnership for U.S. federal income tax purposes) holds our common stock, the tax treatment of a partner will generally depend upon the status of the partner and the activities of the partnership. Non-U.S. holders that are partners of a partnership holding our common stock should consult their tax advisors.

**NON-U.S. HOLDERS CONSIDERING THE PURCHASE OF OUR COMMON STOCK SHOULD CONSULT THEIR OWN TAX ADVISORS CONCERNING THE PARTICULAR UNITED STATES FEDERAL INCOME AND ESTATE TAX CONSEQUENCES OF THE OWNERSHIP OF OUR COMMON STOCK, AS WELL AS THE CONSEQUENCES ARISING UNDER THE LAWS OF ANY OTHER TAXING JURISDICTION.**

#### Distribution on our common stock

Distributions paid on our common stock will be taxable as dividends to the extent paid out of current or accumulated earnings and profits, as determined under the Code. Any portion of a distribution that exceeds our current and accumulated earnings and profits will first be applied to reduce the non-U.S. holder's basis in the common stock, and, to the extent such portion exceeds the non-U.S. holder's basis, the excess will be treated as gain from the disposition of the common stock, the tax treatment of which is discussed below under "Gain on disposition of our common stock."

Dividends paid to a non-U.S. holder of our common stock generally will be subject to United States federal withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. However, dividends that are effectively connected with the conduct of a trade or business by the non-U.S. holder within the United States (and, if required by an applicable income tax treaty, are attributable to a United States permanent establishment) are not subject to United States federal withholding tax, provided certain certification and disclosure requirements are satisfied. Instead, such dividends are subject to United States federal income tax on a net income basis in the same manner as if the non-U.S. holder were a "United States person" as defined in Section 7701(a)(30) of the Code, unless an applicable income tax treaty provides otherwise. Any



such “effectively connected” dividends received by a foreign corporation may, under certain circumstances, be subject to an additional “branch profits tax” at a 30% rate or such lower rate as may be specified by an applicable income tax treaty.

Subject to the discussion below under “FATCA,” a non-U.S. holder who wishes to claim the benefit of an applicable treaty rate and avoid backup withholding, as discussed below, for dividends will be required (a) to complete IRS Form W-8BEN or W-8BEN-E (or other applicable IRS Form) and certify under penalty of perjury that it is not a “United States person” as defined in the Code and is eligible for treaty benefits or (b) if the common stock is held through certain foreign intermediaries, to satisfy the relevant certification requirements of applicable Treasury Regulations. Special certification and other requirements apply to certain non-U.S. holders that are pass-through entities rather than corporations or individuals.

A non-U.S. holder eligible for a reduced rate of United States withholding tax pursuant to an income tax treaty may obtain a refund of any excess amounts withheld by filing an appropriate claim for refund with the IRS.

#### **Gain on disposition of our common stock**

Any gain realized on the disposition of our common stock by a non-U.S. holder generally will not be subject to United States federal income tax unless:

- the gain is effectively connected with a trade or business of the non-U.S. holder in the United States (and, if required by an applicable income tax treaty, is attributable to a United States permanent establishment of the non-U.S. holder);
- the non-U.S. holder is an individual who is present in the United States for 183 days or more in the taxable year of that disposition, and certain other conditions are met; or
- we are or have been a “United States real property holding corporation” for United States federal income tax purposes at any time during the shorter of the five-year period ending on the date of the disposition or such non-U.S. holder’s holding period for our common stock and such non-U.S. holder held (at any time during the shorter of the five-year period ending on the date of the disposition or such non-U.S. holder’s holding period) more than 5% of our common stock.

An individual non-U.S. holder described in the first bullet point immediately above will be subject to tax on the net gain derived from the sale under regular graduated United States federal income tax rates. If a non-U.S. holder that is a foreign corporation falls under the first bullet point immediately above, it will be subject to tax on its net gain in the same manner as if it were a “United States person” as defined in the Code and, in addition, may under certain circumstances be subject to a branch profits tax equal to 30% of its effectively connected earnings and profits or at such lower rate as may be specified by an applicable income tax treaty.

Generally, a corporation is a “United States real property holding corporation” if the fair market value of its United States real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests and its other assets used or held for use in a trade or business (all as determined for United States federal income tax purposes).

We believe we have not been and are not currently a “United States real property holding corporation” for United States federal income tax purposes; however, no assurance can be given that we are not or will not become one in the future. If, however, we are or become a “United States real property holding corporation,” so long as our common stock continues to be regularly traded on an established securities market, only a non-U.S. holder who holds, or held (at any time during the shorter of the five-year period ending on the date of disposition or the non-U.S. holder’s holding period) more than 5% of our common stock will be subject to United States federal income tax on the disposition of the common stock. Non-U.S. holders should consult their own tax advisors about the consequences if we are, or become, a “United States real property holding corporation.”

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#### **Information reporting and backup withholding**

Information returns are required to be filed with the IRS reporting the amount of dividends paid to each non-U.S. holder and the tax withheld with respect to such dividends, regardless of whether withholding was required. Copies of the information returns reporting such dividends and withholding may also be made available to the tax authorities in the country in which the non-U.S. holder resides, under the provisions of an applicable income tax treaty.

A non-U.S. holder will be subject to backup withholding with respect to dividends paid to it unless it certifies under penalty of perjury that it is a non-U.S. holder (and the payor does not have actual knowledge or reason to know that the non-U.S. holder is a “United States person” as defined in the Code), or it otherwise establishes an exemption.

Information reporting and, depending on the circumstances, backup withholding will apply to the proceeds of a sale of our common stock within the United States or conducted through certain United States-related financial intermediaries, unless the non-U.S. holder certifies under penalty of perjury that it is not a “United States person” as defined in the Code (and the payor does not have actual knowledge or reason to know that the non-U.S. holder is a “United States person” as defined in the Code), or it otherwise establishes an exemption.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a non-U.S. holder’s United States federal income tax liability, provided the required information is timely furnished to the IRS.

#### **FATCA**

Sections 1471 to 1474 of the Code (such sections, and the Treasury Regulations and administrative guidance issued thereunder, commonly referred to as “FATCA”) impose a 30% United States withholding tax on certain “withholdable payments” made to a “foreign entity.” “Withholdable payments” include payments of dividends and previously required (as of January 1, 2019) such withholding in respect of certain gross proceeds. However, proposed regulations issued December 13, 2018 and upon which taxpayers may rely, eliminate FATCA withholding for gross proceeds. In general, if a non-U.S. holder is a “foreign financial institution,” the 30% withholding tax will apply to withholdable payments made to it, unless it enters into an agreement with the United States Department of Treasury to collect and provide substantial information regarding its United States account holders, including certain account holders that are foreign entities with United States owners. If it is a “non-financial foreign entity,” FATCA also generally will impose a withholding tax of 30% on withholdable payments made to it unless it provides the withholding agent with a certification that it does not have any “substantial United States owners” or a certification identifying its direct and indirect substantial United States owners. Intergovernmental agreements between the United States and a non-U.S. holder’s resident country may modify the foregoing requirements. Foreign entities located in jurisdictions that have entered into intergovernmental agreements with the U.S. in connection with FATCA may be subject to different rules.

Non-U.S. holders should consult their own tax advisors regarding the impact of FATCA on their ownership and disposition of shares of our common stock and the potential applicability of any intergovernmental agreements.

## UNDERWRITING

Aegis Capital Corp. is acting as the representative of the underwriters of the offering. We have entered into an underwriting agreement dated November 9, 2021, with the representative. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters named below and the underwriters named below have agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus, the following number of shares of our common stock:

Underwriter	Number of Shares
Aegis Capital Corp.	

The underwriters are committed to purchase all the shares of common stock offered by us other than those covered by the option to purchase additional shares described below, if they purchase any shares. The obligations of the underwriters may be terminated upon the occurrence of certain events specified in the underwriting agreement. Furthermore, pursuant to the underwriting agreement, the underwriters' obligations are subject to customary conditions, representations and warranties contained in the underwriting agreement, such as receipt by the underwriters of officers' certificates and legal opinions.

We have agreed to indemnify the underwriters against specified liabilities, including liabilities under the Securities Act of 1933, as amended, and to contribute to payments the underwriters may be required to make in respect thereof.

The underwriters are offering the common stock, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel and other conditions specified in the underwriting agreement. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

The underwriters propose to offer the common stock offered by us to the public at the public offering price set forth on the cover of this prospectus. In addition, the underwriters may offer some of the common stock to other securities dealers at such price less a concession of \$ per share. After the initial offering, the public offering price and concession to dealers may be changed.

We have granted the underwriters an over-allotment option. This option, which is exercisable for up to 45 days after the date of this prospectus, permits the underwriters to purchase a maximum of additional shares of common stock from us to cover over-allotments. If the underwriters exercise all or part of this option, they will purchase shares of common stock covered by the option at the public offering price that appears on the cover page of this prospectus, less the underwriting discount. If this option is exercised in full, the total price to the public will be \$ .

*Discounts and Commissions.* The following table shows the public offering price, underwriting discount, non-accountable underwriters' expense allowance and proceeds, before expenses, to us. The information assumes either no exercise or full exercise by the underwriters of their over-allotment option.

	Per Share	Total	
		Without Over- Allotment	With Over- Allotment
Public offering price	\$	\$	\$
Underwriting discount (6%)	\$		
Proceeds, before expenses, to us	\$	\$	\$

We have also agreed to pay all expenses relating to the offering, including (a) all filing fees and expenses relating to the registration of the shares to be sold in the offering (including shares sold upon exercise of the underwriters' over-allotment option) with the Securities and Exchange Commission; (b) all fees associated with the review of the offering by FINRA and all fees and expenses relating to the listing of such shares on the Nasdaq Capital Market; (c) all fees, expenses and disbursements relating to the registration, qualification or exemption of securities offered under the "blue sky" securities laws designated by the underwriters; (d) all fees, expenses and disbursements relating to the registration, qualification or exemption of securities offered under the securities laws of foreign jurisdictions designated by the underwriters; (e) transfer and/or stamp taxes, if any, payable upon the transfer of the shares from the Company to the representative; (f) fees and expenses of our accountants; and (g) fees and expenses of the representative, including representative's legal counsel, not to exceed \$25,000.

We estimate that the total expenses of the offering, excluding underwriting discount and non-accountable expense allowance, will be approximately \$ .

*Discretionary Accounts.* The underwriters do not intend to confirm sales of the securities offered hereby to any accounts over which they have discretionary authority.

*Lock-Up Agreements.* Pursuant to certain "lock-up" agreements, (a) our executive officers and directors as of the pricing date of the offering, have agreed, subject to certain exceptions, not to offer, issue, sell, contract to sell, encumber, grant any option for the sale of or otherwise dispose of any securities of the Company without the prior written consent of the representative, for a period of 45 days from the date of the offering, and (b) we, and any successor, have agreed, subject to certain exceptions, not to for a period of 30 days from the date of the pricing of the offering (1) offer, sell or otherwise transfer or dispose of, directly or indirectly, any shares of capital stock of the Company or (2) file or caused to be filed any registration statement with the SEC relating to the offering of any shares of our capital stock or any securities convertible into or exercisable or exchangeable for shares of our capital stock.

This lock-up provision applies to common stock and to securities convertible into or exchangeable or exercisable for common stock. It also applies to common stock owned now or acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition. The exceptions permit, among other things and subject to restrictions, the issuance of common stock upon the exercise of outstanding stock options and warrants or other outstanding convertible securities.

*Right of First Refusal.* The representative shall have a right of first refusal to act as sole book-running manager for any and all future public equity offerings of the Company or any successor until six (6) months after the closing date of the offering.

*Electronic Offer, Sale and Distribution of Shares.* A prospectus in electronic format may be made available on the websites maintained by one or more of the underwriters or selling group members, if any, participating in this offering and one or more of the underwriters participating in this offering may distribute prospectuses electronically. The representative may agree to allocate a number of shares to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the underwriters and selling group members that will make internet distributions on the same basis as other allocations. Other than the prospectus in electronic format, the information on these websites is not part of this prospectus or the registration statement of which this prospectus forms a part, has not been approved or endorsed by us or any underwriter in its capacity as underwriter, and should not be relied upon by investors.

*Other Relationships.* Certain of the underwriters and their affiliates have provided, and may in the future provide, various investment banking, commercial banking and other financial services for us and our affiliates for which they have received, and may in the future receive, customary fees; however, except as disclosed in this prospectus, we have no present arrangements with any of the underwriters for any further services.

*Stabilization.* In connection with this offering, the underwriters may engage in stabilizing transactions, overallotment transactions, syndicate covering transactions, penalty bids and purchases to cover positions created by short sales.

- Stabilizing transactions permit bids to purchase shares so long as the stabilizing bids do not exceed a specified maximum, and are engaged in for the purpose of preventing or retarding a decline in the market price of the shares while the offering is in progress.
- Overallotment transactions involve sales by the underwriters of shares in excess of the number of shares the underwriters are obligated to purchase. This creates a syndicate short position which may be either a covered short position or a naked short position. In a covered short position, the number of shares over-allotted by the underwriters is not greater than the number of shares that they may purchase in the overallotment option. In a naked short position, the number of shares involved is greater than the number of shares in the overallotment option. The underwriters may close out any short position by exercising their overallotment option and/or purchasing shares in the open market.
- Syndicate covering transactions involve purchases of shares in the open market after the distribution has been completed in order to cover syndicate short positions. In determining the source of shares to close out the short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared with the price at which they may purchase shares through exercise of the overallotment option. If the underwriters sell more shares than could be covered by exercise of the overallotment option and, therefore, have a naked short position, the position can be closed out only by buying shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that after pricing there could be downward pressure on the price of the shares in the open market that could adversely affect investors who purchase in the offering.
- Penalty bids permit the representative to reclaim a selling concession from a syndicate member when the shares originally sold by that syndicate member are purchased in stabilizing or syndicate covering transactions to cover syndicate short positions.

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These stabilizing transactions, syndicate covering transactions and penalty bids may have the effect of raising or maintaining the market price of our shares or common stock or preventing or retarding a decline in the market price of our shares or common stock. As a result, the price of our common stock in the open market may be higher than it would otherwise be in the absence of these transactions. Neither we nor the underwriters make any representation or prediction as to the effect that the transactions described above may have on the price of our common stock. These transactions may be effected on the Nasdaq Capital Market.

*Passive Market Making.* In connection with this offering, underwriters and selling group members may engage in passive market making transactions in our common stock on the Nasdaq Capital Market in accordance with Rule 103 of Regulation M under the Exchange Act, during a period before the commencement of offers or sales of the shares and extending through the completion of the distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, that bid must then be lowered when specified purchase limits are exceeded.

#### **Offer restrictions outside the United States**

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

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### **LEGAL MATTERS**

The validity of the common stock offered by this prospectus supplement and the accompanying prospectus will be passed upon for us by Alston & Bird LLP, New York, New York. The underwriters are being represented in connection with this offering by Kaufman & Canoles, P.C., Richmond, Virginia.

### **EXPERTS**

The financial statements of Avenue Therapeutics, Inc. as of December 31, 2020 and 2019 and for each of the two years in the period ended December 31, 2020 incorporated by reference in this prospectus supplement and in the Registration Statement have been so incorporated in reliance on the report of BDO USA, LLP, an independent registered public accounting firm, incorporated herein by reference, given on the authority of said firm as experts in auditing and accounting. The report on the financial statements contains an explanatory paragraph regarding the Company's ability to continue as a going concern.

### **WHERE YOU CAN FIND MORE INFORMATION**

We are a public company and file reports with the SEC on an annual basis using Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K. Additionally, the SEC maintains a website that contains annual, quarterly, and current reports, proxy statements, and other information that issuers (including us) file electronically with the SEC. The SEC's website address is <http://www.sec.gov>. You can also obtain copies of materials we file with the SEC from our Internet website found at [www.avenuetx.com](http://www.avenuetx.com). Our stock is quoted on the Nasdaq Capital Market under the symbol "ATXI". We have not incorporated by reference into this prospectus supplement the information on our website, and you should not consider it to be a part of this prospectus supplement.

### **INCORPORATION OF CERTAIN INFORMATION BY REFERENCE**

The SEC allows us to "incorporate by reference" the information we file with them which means that we can disclose important information to you by referring you to those documents instead of having to repeat the information in this prospectus supplement and accompanying prospectus. The information incorporated by reference is considered to be part of this prospectus supplement and accompanying prospectus, and later information that we file with the SEC will automatically update and supersede this information. This prospectus supplement incorporates by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(e), 14 or 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act") (1) after the date of the initial registration statement, as amended, and prior to effectiveness of the

registration statement, and (2) after the date of this prospectus supplement and prior to the termination of this offering. Such information will automatically update and supersede the information contained in this prospectus supplement and the documents listed below; provided, however, that we are not, unless specifically indicated, incorporating any information furnished under Item 2.02 or Item 7.01 of any current report on Form 8-K, whether listed below or filed in the future, or related exhibits furnished pursuant to Item 9.01 of Form 8-K:

- a) Our Annual Report on Form 10-K for the year ended December 31, 2020 filed with the SEC on [March 31, 2021](#);
- b) Our Quarterly Reports on Form 10-Q for the quarters ended June 30, 2021, filed with the SEC on [August 16, 2021](#), and March 31, 2021, filed with the SEC on [May 17, 2021](#); and
- c) Our Current Reports on Form 8-K filed with the SEC on [January 8, 2021](#), [February 16, 2021](#), [March 1, 2021](#), [April 5, 2021](#), [May 3, 2021](#), [June 14, 2021](#), [July 15, 2021](#), [July 29, 2021](#), [August 27, 2021](#), [September 1, 2021](#), [September 3, 2021](#), [September 21, 2021](#), [October 25, 2021](#), and [November 4, 2021](#).

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, including all such documents we may file with the SEC after the date of the initial registration statement and prior to the effectiveness of the registration statement, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus supplement and deemed to be part of this prospectus supplement from the date of the filing of such reports and documents.

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## PROSPECTUS

\$3,000,000



**Common Stock**  
**Preferred Stock**  
**Warrants**  
**Debt Securities**  
**Units**

The following are types of securities that we may offer, issue and sell from time to time, together or separately:

- shares of our common stock;
- shares of our preferred stock;
- warrants;
- debt securities; and
- units consisting of any combination of our common stock, preferred stock, warrants or debt securities.

We may offer these securities in amounts, at prices, and on terms determined at the time of offering, up to an aggregate amount of \$3,000,000. We may sell these securities directly to you through agents we select or through underwriters and dealers we select. If we use agents, underwriters or dealers to sell these securities, we will name them and describe their compensation in a prospectus supplement. See "Plan of Distribution." You should read this prospectus and any prospectus supplement carefully before you invest.

This prospectus provides a general description of the securities we may offer. Each time we sell securities, we will provide specific terms of the securities offered in a supplement to this prospectus. The prospectus supplement may also add, update or change information contained in this prospectus. You should read this prospectus and the applicable prospectus supplement carefully, together with additional information described under the heading "Where You Can Find More Information," before you invest in any securities. This prospectus may not be used to consummate a sale of securities unless accompanied by the applicable prospectus supplement.

Our common stock is traded on the Nasdaq Capital Market under the symbol "ATXI." On September 21, 2021, the per share closing price of our common stock as reported on the Nasdaq Capital Market was \$1.55 per share. The aggregate market value of our outstanding common stock held by non-affiliates, computed by reference to the last sold price of \$1.55 per share on the NASDAQ Capital Market on September 21, 2021, is approximately \$10.4 million based on 16,793,068 shares of common stock outstanding, of which 6,677,654 are held by non-affiliates. We have not offered or sold any securities pursuant to General Instruction I.B.6 of Form S-3 during the 12 calendar month period that ends on, and includes, the date of this prospectus.

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act and will therefore be subject to reduced reporting requirements.

**Investing in our common stock involves certain risks.** See "Risk Factors" in our Quarterly Report on Form 10-Q for the quarter ended June 30, 2021 which has been filed with the SEC and is incorporated by reference into this prospectus. You should read the prospectus, any prospectus supplement relating to any specific offering of securities, and all information incorporated by reference herein and therein carefully before you make your investment decision.

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

The date of this prospectus is \_\_\_\_\_, 2021

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### ABOUT THIS PROSPECTUS

In this prospectus, unless the context suggests otherwise, references to “Avenue Therapeutics,” “Avenue,” the “Company,” “we,” “us” and “our” refer to Avenue Therapeutics, Inc.

This prospectus is part of a “shelf” registration statement that we filed with the SEC. By using a shelf registration statement, we may sell our securities, as described in this prospectus, from time to time in one or more offerings. This prospectus provides you with a general description of the securities offered by us. Each time we sell securities, we will provide a prospectus supplement to this prospectus that contains specific information about the terms of such offering. The prospectus or prospectus supplement may also add, update or change information contained in this prospectus.

You should rely only on the information contained or incorporated by reference in this prospectus and any prospectus supplement or issuer free writing prospectus relating to a particular offering. No person has been authorized to give any information or make any representations in connection with this offering other than those contained or incorporated by reference in this prospectus, any accompanying prospectus supplement and any related issuer free writing prospectus in connection with the offering described herein and therein, and, if given or made, such information or representations must not be relied upon as having been authorized by us. Neither this prospectus nor any prospectus supplement nor any related issuer free writing prospectus shall constitute an offer to sell or a solicitation of an offer to buy offered securities in any jurisdiction in which it is unlawful for such person to make such an offering or solicitation. This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the securities, you should refer to the registration statement, including its exhibits. You should read the entire prospectus and any prospectus supplement and any related issuer free writing prospectus, as well as the documents incorporated by reference into this prospectus or any prospectus supplement or any related issuer free writing prospectus, before making an investment decision. Neither the delivery of this prospectus or any prospectus supplement or any issuer free writing prospectus nor any sale made hereunder shall under any circumstances imply that the information contained or incorporated by reference herein or in any prospectus supplement or issuer free writing prospectus is correct as of any date subsequent to the date hereof or of such prospectus supplement or issuer free writing prospectus, as applicable.

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

## PROSPECTUS SUMMARY

This summary provides an overview of selected information contained elsewhere or incorporated by reference in this prospectus and does not contain all of the information you should consider before investing in our securities. You should carefully read the prospectus, the information incorporated by reference and the registration statement of which this prospectus is a part in their entirety before investing in our securities, including the information discussed under "Risk Factors" in this prospectus and the documents incorporated by reference and our financial statements and notes thereto that are incorporated by reference in this prospectus. As used in this prospectus, unless the context otherwise indicates, the terms "we," "our," "us," or "the Company" refers to Avenue Therapeutics, Inc., a Delaware corporation.

We are a specialty pharmaceutical company that seeks to develop and commercialize our product principally for use in the acute/intensive care hospital setting. Our current product candidate is intravenous ("IV") Tramadol, for the treatment of post-operative acute pain. Under the terms of certain agreements described herein, we have an exclusive license to develop and commercialize IV Tramadol in the United States. In 2016, we completed a pharmacokinetic study for IV Tramadol in healthy volunteers as well as an end of phase 2 meeting with the U.S. Food and Drug Administration ("FDA"). In the third quarter of 2017, we initiated a Phase 3 development program of IV Tramadol for the management of post-operative pain. In December 2019, we submitted a New Drug Application ("NDA") for IV Tramadol and received a Complete Response Letter from the FDA in October 2020. In February 2021, we resubmitted the NDA for IV Tramadol. The FDA assigned a Prescription Drug User Fee Act goal date of April 12, 2021 for the resubmitted NDA for IV Tramadol. On June 14, 2021, we announced that we had received a second Complete Response Letter from the FDA regarding our NDA for IV Tramadol. We continue to pursue regulatory approval for IV Tramadol and had a Type A meeting with the FDA in July 2021. We submitted a formal dispute resolution request ("FDRR") to the Office of Neuroscience of the FDA on July 27, 2021. On August 26, 2021, we received an Appeal Denied Letter from the Office of Neuroscience of the FDA. On August 31, 2021, we submitted a FDRR to the Office of New Drugs of the FDA and a response will be provided by October 28, 2021 by the Office of New Drugs of the FDA. To date, we have not received approval for the sale of our product candidate in any market and, therefore, have not generated any sales revenue from our product candidate.

On November 12, 2018, we entered into a Stock Purchase and Merger Agreement ("SPMA") with InvaGen Pharmaceuticals Inc. ("InvaGen"), and Madison Pharmaceuticals, Inc. pursuant to which we agreed to sell the Company in a two-stage transaction. In the first stage, InvaGen agreed to purchase, for \$35 million, common shares representing 33.3% of the fully diluted capitalization of the Company. In the second stage, InvaGen would acquire the remaining issued and outstanding capital stock of the Company for approximately \$180 million in a reverse subsidiary merger transaction (the "Merger Transaction"). The SPMA was approved by a majority of our stockholders, including a majority of its non-affiliated stockholders, at its special shareholder meeting on February 6, 2019. On February 8, 2019, InvaGen acquired 5,833,333 shares of the Company's common stock at \$6.00 per share (the "Stock Purchase Transaction") for net proceeds of \$31.5 million after deducting commission fees and other offering costs, representing a 33.3% stake in the Company's capital stock on a fully diluted basis.

Consummation of the Merger Transaction is conditioned upon, among other things, the FDA's approval of IV Tramadol, its labeling and scheduling, and the absence of certain other restrictions in effect with respect to IV Tramadol. Pursuant to the SPMA, if FDA approval of IV Tramadol was not obtained on or before April 30, 2021, InvaGen would not be subject to the mandatory closing obligations set forth in the SPMA with respect to the Merger Transaction. As the Company did not receive approval from the FDA for IV Tramadol on or before April 30, 2021, InvaGen is no longer subject to the mandatory closing obligations under the SPMA, but retains an option to complete the Merger Transaction until October 31, 2021 (the time following which the Company can choose to terminate the SPMA), and also retains the option to terminate the SPMA.

In the event that InvaGen does not exercise its right to terminate the SPMA, certain restrictions relating to the Company's ability to raise capital and explore strategic alternatives, among other things, could exist through October 31, 2021, the time following which the Company can choose to terminate the SPMA. In the event of termination of the SPMA, InvaGen will retain certain rights pursuant to the Stockholder's Agreement entered into on November 12, 2018 between the Company and InvaGen. These rights exist as long as InvaGen maintains at least 75% of the common shares acquired in the Stock Purchase Transaction and include among other things, the right to restrict the Company from certain equity issuances and changes to the Company's capital stock without obtaining InvaGen's prior written consent.

The aggregate consideration to be paid by InvaGen under the SPMA if it completes the Merger Transaction is \$215 million in cash (a portion of which was already paid in connection with the Stock Purchase Transaction), subject to certain potential reductions, which InvaGen intends to have sufficient immediately available funds to pay in the event that payment is required. In addition, we are subject to certain lock-up restrictions and agreed not to (subject to customary exceptions), during the period commencing at the signing of the SPMA until the Merger Transaction, issue, buy, sell, or otherwise subject to a security interest, pledge, hypothecation, mortgage or lien, any securities of the Company.

To date, we have not received approval for the sale of our product candidate in the U.S. market and, therefore, have not generated any product sales. In addition, we have incurred substantial operating losses since our inception, and expect to continue to incur significant operating losses for the foreseeable future and may never become profitable as we develop and seek regulatory approval for IV Tramadol in the U.S.

**Our principal executive offices are located at 1140 Avenue of the Americas, Floor 9, New York, New York 10036, and our telephone number is 781-652-4500. We maintain a website on the Internet at [www.avenuetx.com](http://www.avenuetx.com) and our e-mail address is [info@avenuetx.com](mailto:info@avenuetx.com). Our Internet website, and the information contained on it, are not to be considered part of this prospectus.**

We are a majority controlled subsidiary of Fortress Biotech, Inc. ("Fortress").

## RISK FACTORS

An investment in our securities involves a high degree of risk. The prospectus supplement applicable to each offering of our securities will contain a discussion of the risks applicable to an investment in our securities. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading "Risk Factors" in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. Each of the referenced risks and uncertainties could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities.

## FORWARD-LOOKING STATEMENTS

This prospectus includes statements that are, or may be deemed, "forward-looking statements." In some cases, these forward-looking statements can be identified by the use of forward-looking terminology, including the terms "believes," "estimates," "anticipates," "expects," "plans," "intends," "may," "could," "might," "will," "should," "approximately" or, in each case, their negative or other variations thereon or comparable terminology, although not all forward-looking statements contain these words. They

appear in a number of places throughout this prospectus and include statements regarding our intentions, beliefs, projections, outlook, analyses or current expectations concerning, among other things, our history of net operating losses and uncertainty regarding our ability to obtain regulatory approval from the FDA for our product candidate, our ability to obtain capital and achieve profitability, our ability to develop and commercialize our product candidate, our ability to obtain, perform under and maintain financing and strategic agreements and relationships, our ability to comply with ongoing regulatory requirements, our ability to successfully operate in a competitive industry and gain market acceptance by physician, provider, patient, and payor communities, our reliance on third parties, unstable economic or market conditions, our ability to adapt with the COVID-19 outbreak and its potential impact on our employees' and consultants' ability to complete work in a timely manner and our ability to obtain and adequately protect intellectual property rights for our product candidate.

By their nature, forward-looking statements involve risks and uncertainties because they relate to events, competitive dynamics, and healthcare, regulatory and scientific developments and depend on the economic circumstances that may or may not occur in the future or may occur on longer or shorter timelines than anticipated. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus, we caution you that forward-looking statements are not guarantees of future performance and that our actual results of operations, financial condition and liquidity, and the development of the industry in which we operate may differ materially from the forward-looking statements contained in this prospectus. In addition, even if our results of operations, financial condition and liquidity, and the development of the industry in which we operate are consistent with the forward-looking statements contained in this prospectus, they may not be predictive of results or developments in future periods. The forward-looking statements contained in this prospectus reflect our views and assumptions only as of the date of this prospectus. Except as required by law, we assume no responsibility for updating any forward-looking statements. We qualify all of our forward-looking statements by these cautionary statements. In addition, with respect to all of our forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

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#### USE OF PROCEEDS

Unless otherwise indicated in the prospectus supplement, the net proceeds from the sale of securities offered by this prospectus will be used for general corporate purposes and working capital requirements, which may include, among other things, the advancement of our product candidate to obtain regulatory approval from the FDA, and in the event of FDA approval of our product candidate, towards the milestone payments due to our licensor and supplier upon FDA approval of our product candidate. We have not determined the amounts we plan to spend on the areas listed above or the timing of these expenditures, and we have no current plans with respect to acquisitions as of the date of this prospectus. As a result, unless otherwise indicated in the prospectus supplement, our management will have broad discretion to allocate the net proceeds of the offerings. Pending their ultimate use, we intend to invest the net proceeds in a variety of securities, including commercial paper, government and non-government debt securities and/or money market funds that invest in such securities.

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#### DESCRIPTION OF SECURITIES WE MAY OFFER

The descriptions of the securities contained in this prospectus, together with the applicable prospectus supplements, summarize all the material terms and provisions of the various types of securities that we may offer. We will describe in the applicable prospectus supplement relating to any securities the particular terms of the securities offered by that prospectus supplement. If indicated in the applicable prospectus supplement, the terms of the securities may differ from the terms we have summarized below. We will also include information in the prospectus supplement, where applicable, about material United States federal income tax considerations relating to the securities, and the securities exchange, if any, on which the securities will be listed. This prospectus may not be used to consummate a sale of securities unless it is accompanied by a prospectus supplement.

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#### DESCRIPTION OF CAPITAL STOCK

The following description summarizes the material terms of our capital stock as of the date of this prospectus. Because it is only a summary, it does not contain all the information that may be important to you. For a complete description of our capital stock, you should refer to our Third Amended and Restated Certificate of Incorporation and our Amended and Restated Bylaws, and to the provisions of applicable Delaware law.

Our authorized capital stock consists of 50,000,000 shares of common stock, with \$0.0001 par value, and 2,000,000 shares of Preferred Stock, with \$0.0001 par value, of which 250,000 have been designated as Class A Preferred Stock and the remainder of which are undesignated Preferred Stock.

As of September 21, 2021, there were 16,793,068 shares of our common stock outstanding held by 48 record stockholders.

##### **Common Stock**

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our Board of Directors, subject to any preferential dividend rights of outstanding preferred stock.

In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Our common stock is traded on the Nasdaq Capital Market under the symbol "ATXI." The transfer agent and registrar for our common stock is VStock Transfer, LLC.

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## DESCRIPTION OF PREFERRED STOCK

### Class A Preferred Stock

Class A Preferred Stock is identical to our common stock other than as to voting rights, the election of directors for a definite period, conversion rights and the PIK Dividend right (as described below). On any matter presented to our stockholders for their action or consideration at any meeting of our stockholders (or by written consent of stockholders in lieu of meeting), each holder of outstanding shares of Class A Preferred Stock will be entitled to cast for each share of Class A Preferred Stock held by such holder as of the record date for determining stockholders entitled to vote on such matter, the number of votes that is equal to one and one-tenth (1.1) times a fraction, the numerator of which is the sum of (A) the shares of outstanding common stock and (B) the whole shares of common stock in to which the shares of outstanding Class A Preferred Stock are convertible and the denominator of which is the number of shares of outstanding Class A Preferred Stock, or the Class A Preferred Stock Ratio. Thus, the Class A Preferred Stock will at all times constitute a voting majority.

For a period of ten years from the date of the first issuance of shares of Class A Preferred Stock, or the Class A Director Period, the holders of record of the shares of Class A Preferred Stock (or other capital stock or securities issued upon conversion of or in exchange for the Class A Preferred Stock), exclusively and as a separate class, shall be entitled to appoint or elect the majority of our directors, or the Class A Directors. Thus, the Class A Preferred Stock will be entitled to elect the majority of the Board of Directors during the Class A Director Period.

The holders of the outstanding shares of Class A Preferred Stock shall receive on January 1 of each year, each a PIK Dividend Payment Date, after the original issuance date of the Class A Preferred Stock until the date all outstanding Class A Preferred Stock is converted into common stock or redeemed (and the purchase price is paid in full), pro rata per share dividends paid in additional fully paid and nonassessable shares of common stock, such dividend being herein called PIK Dividends, such that the aggregate number of shares of common stock issued pursuant to such PIK Dividend is equal to 2.5% of our fully-diluted outstanding capitalization on the date that is one business day prior to any PIK Dividend Payment Date, or PIK Record Date. In the event the Class A Preferred Stock converts into common stock, the holders shall receive all PIK Dividends accrued through the date of such conversion. This PIK Dividend was waived in connection with the Waiver Agreement signed on November 12, 2018 between Avenue, Fortress and InvaGen.

Each share of Class A Preferred Stock is convertible, at the option of the holder, into one fully paid and nonassessable share of common stock, or the Conversion Ratio, subject to certain adjustments.

### Undesignated Preferred Stock

The undesignated Preferred Stock may be issued from time to time in one or more series. Our Board of Directors is authorized to determine or alter the dividend rights, dividend rate, conversion rights, voting rights, rights and terms of redemption (including sinking fund provisions, if any), the redemption price or prices, the liquidation preferences and other designations, powers, preferences and relative, participating, optional or other special rights, if any, and the qualifications, limitations and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to fix the number of shares of any series of Preferred Stock (but not below the number of shares of any such series then outstanding).

## DESCRIPTION OF WARRANTS

We may issue warrants to purchase shares of our common stock and/or preferred stock in one or more series together with other securities or separately, as described in each applicable prospectus supplement. As of September 21, 2021, there were 15,576 shares of common stock that may be issued upon exercise of outstanding warrants.

The prospectus supplement relating to any warrants we offer will include specific terms relating to the offering. These terms will include some or all of the following:

- the title of the warrants;
- the aggregate number of warrants offered;
- the designation, number and terms of the shares of common stock purchasable upon exercise of the warrants and procedures by which those numbers may be adjusted;
- the exercise price of the warrants;
- the dates or periods during which the warrants are exercisable;
- the designation and terms of any securities with which the warrants are issued;
- if the warrants are issued as a unit with another security, the date on and after which the warrants and the other security will be separately transferable;
- if the exercise price is not payable in U.S. dollars, the foreign currency, currency unit or composite currency in which the exercise price is denominated;
- any minimum or maximum amount of warrants that may be exercised at any one time;
- any terms relating to the modification of the warrants;
- any terms, procedures and limitations relating to the transferability, exchange or exercise of the warrants; and
- any other specific terms of the warrants.

## DESCRIPTION OF DEBT SECURITIES

We may offer debt securities which may be senior, subordinated or junior subordinated and may be convertible. Unless otherwise specified in the applicable prospectus supplement, our debt securities will be issued in one or more series under an indenture to be entered into between us and a trustee. We will issue the debt securities offered by this prospectus and any accompanying prospectus supplement under an indenture to be entered into between us and the trustee identified in the applicable prospectus



supplement. The terms of the debt securities will include those stated in the indenture and those made part of the indenture by reference to the Trust Indenture Act of 1939, as in effect on the date of the indenture. We have filed a copy of the form of indenture as an exhibit to the registration statement in which this prospectus is included. The indenture will be subject to and governed by the terms of the Trust Indenture Act of 1939.

The following description briefly sets forth certain general terms and provisions of the debt securities that we may offer. The particular terms of the debt securities offered by any prospectus supplement and the extent, if any, to which these general provisions may apply to the debt securities, will be described in the related prospectus supplement. Accordingly, for a description of the terms of a particular issue of debt securities, reference must be made to both the related prospectus supplement and to the following description.

#### **Debt Securities**

The aggregate principal amount of debt securities that may be issued under the indenture is unlimited. The debt securities may be issued in one or more series as may be authorized from time to time pursuant to a supplemental indenture entered into between us and the trustee or an order delivered by us to the trustee. For each series of debt securities we offer, a prospectus supplement accompanying this prospectus will describe the following terms and conditions of the series of debt securities that we are offering, to the extent applicable:

- title and aggregate principal amount;
- whether the debt securities will be senior, subordinated or junior subordinated;
- applicable subordination provisions, if any;
- provisions regarding whether the debt securities will be convertible or exchangeable into other securities or property of the Company or any other person;
- percentage or percentages of principal amount at which the debt securities will be issued;
- maturity date(s);
- interest rate(s) or the method for determining the interest rate(s);
- whether interest on the debt securities will be payable in cash or additional debt securities of the same series;
- dates on which interest will accrue or the method for determining dates on which interest will accrue and dates on which interest will be payable;
- whether the amount of payment of principal of, premium, if any, or interest on the debt securities may be determined with reference to an index, formula or other method;
- redemption, repurchase or early repayment provisions, including our obligation or right to redeem, purchase or repay debt securities under a sinking fund, amortization or analogous provision;
- if other than the debt securities' principal amount, the portion of the principal amount of the debt securities that will be payable upon declaration of acceleration of the maturity;
- authorized denominations;
- form;

- amount of discount or premium, if any, with which the debt securities will be issued, including whether the debt securities will be issued as "original issue discount" securities;
- the place or places where the principal of, premium, if any, and interest on the debt securities will be payable;
- where the debt securities may be presented for registration of transfer, exchange or conversion;
- the place or places where notices and demands to or upon the Company in respect of the debt securities may be made;
- whether the debt securities will be issued in whole or in part in the form of one or more global securities;
- if the debt securities will be issued in whole or in part in the form of a book-entry security, the depository or its nominee with respect to the debt securities and the circumstances under which the book-entry security may be registered for transfer or exchange or authenticated and delivered in the name of a person other than the depository or its nominee;
- whether a temporary security is to be issued with respect to such series and whether any interest payable prior to the issuance of definitive securities of the series will be credited to the account of the persons entitled thereto;
- the terms upon which beneficial interests in a temporary global security may be exchanged in whole or in part for beneficial interests in a definitive global security or for individual definitive securities;
- the guarantors, if any, of the debt securities, and the extent of the guarantees and any additions or changes to permit or facilitate guarantees of such debt securities;
- any covenants applicable to the particular debt securities being issued;
- any defaults and events of default applicable to the debt securities, including the remedies available in connection therewith;
- currency, currencies or currency units in which the purchase price for, the principal of and any premium and any interest on, such debt securities will be payable;

- time period within which, the manner in which and the terms and conditions upon which the Company or the purchaser of the debt securities can select the payment currency;
- securities exchange(s) on which the debt securities will be listed, if any;
- whether any underwriter(s) will act as market maker(s) for the debt securities;
- extent to which a secondary market for the debt securities is expected to develop;
- provisions relating to defeasance;
- provisions relating to satisfaction and discharge of the indenture;
- any restrictions or conditions on the transferability of the debt securities;
- provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;
- any addition or change in the provisions related to compensation and reimbursement of the trustee;
- provisions, if any, granting special rights to holders upon the occurrence of specified events;
- whether the debt securities will be secured or unsecured, and, if secured, the terms upon which the debt securities will be secured and any other additions or changes relating to such security; and
- any other terms of the debt securities that are not inconsistent with the provisions of the Trust Indenture Act (but may modify, amend, supplement or delete any of the terms of the indenture with respect to such series of debt securities).

## General

One or more series of debt securities may be sold as “original issue discount” securities. These debt securities would be sold at a substantial discount below their stated principal amount, bearing no interest or interest at a rate which at the time of issuance is below market rates. One or more series of debt securities may be variable rate debt securities that may be exchanged for fixed rate debt securities.

United States federal income tax consequences and special considerations, if any, applicable to any such series will be described in the applicable prospectus supplement.

Debt securities may be issued where the amount of principal and/or interest payable is determined by reference to one or more currency exchange rates, commodity prices, equity indices or other factors. Holders of such debt securities may receive a principal amount or a payment of interest that is greater than or less than the amount of principal or interest otherwise payable on such dates, depending upon the value of the applicable currencies, commodities, equity indices or other factors. Information as to the methods for determining the amount of principal or interest, if any, payable on any date, the currencies, commodities, equity indices or other factors to which the amount payable on such date is linked and certain additional United States federal income tax considerations will be set forth in the applicable prospectus supplement.

The term “debt securities” includes debt securities denominated in U.S. dollars or, if specified in the applicable prospectus supplement, in any other freely transferable currency or units based on or relating to foreign currencies.

We expect most debt securities to be issued in fully registered form without coupons and in denominations of \$2,000 and any integral multiples thereof. Subject to the limitations provided in the indenture and in the prospectus supplement, debt securities that are issued in registered form may be transferred or exchanged at the principal corporate trust office of the trustee, without the payment of any service charge, other than any tax or other governmental charge payable in connection therewith.

## Global Securities

The debt securities of a series may be issued in whole or in part in the form of one or more global securities that will be deposited with, or on behalf of, a depository identified in the prospectus supplement. Global securities will be issued in registered form and in either temporary or definitive form. Unless and until it is exchanged in whole or in part for the individual debt securities, a global security may not be transferred except as a whole by the depository for such global security to a nominee of such depository or by a nominee of such depository to such depository or another nominee of such depository or by such depository or any such nominee to a successor of such depository or a nominee of such successor. The specific terms of the depository arrangement with respect to any debt securities of a series and the rights of and limitations upon owners of beneficial interests in a global security will be described in the applicable prospectus supplement.

## Governing Law

The indenture and the debt securities shall be construed in accordance with and governed by the laws of the State of New York.

## DESCRIPTION OF UNITS

We may issue, in one more series, units comprised of shares of our common stock and/or preferred stock, warrants to purchase common stock and/or preferred stock, debt securities or any combination of those securities. Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date.

We may evidence units by unit certificates that we issue under a separate agreement. We may issue the units under a unit agreement between us and one or more unit agents. If we elect to enter into a unit agreement with a unit agent, the unit agent will act solely as our agent in connection with the units and will not assume any obligation or relationship of agency or trust for or with any registered holders of units or beneficial owners of units. We will indicate the name and address and other information regarding the unit agent in the applicable prospectus supplement relating to a particular series of units if we elect to use a unit agent.

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

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement that differ from those described herein; and
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

The other provisions regarding our common stock, preferred stock, warrants and debt securities as described in this section will apply to each unit to the extent such unit consists of shares of our common stock, warrants and/or debt securities.

## PLAN OF DISTRIBUTION

We may sell the securities covered in this prospectus in one or more of the following ways:

- through underwriters or dealers;
- in short or long transactions;
- directly to a limited number of purchasers or to a single purchaser;
- through agents, including via an at-the-market program; or
- through a combination of any of these methods of sale.

Each time that we use this prospectus to sell securities, we will also provide a prospectus supplement that contains the specific terms of the offering. The prospectus supplement will set forth the terms of the offering of the securities, including:

- the name or names of any underwriters, dealers or agents and the amounts of any securities underwritten or purchased by each of them; and
- the purchase price of the securities being offered and the proceeds to us and any discounts, commissions or concessions allowed or reallocated or paid to dealers.

Any public offering price and any discounts or concessions allowed or reallocated or paid to dealers may be changed from time to time.

If underwriters are used in the sale of any securities, the securities will be acquired by the underwriters for their own account and may be resold from time to time in one or more transactions, including negotiated transactions, at a fixed public offering price or at varying prices determined at the time of sale. The securities may be either offered to the public through underwriting syndicates represented by managing underwriters, or directly by underwriters. Generally, the underwriters' obligations to purchase the securities will be subject to certain conditions precedent. The underwriters will be obligated to purchase all of the securities if they purchase any of securities. Only underwriters named in the applicable prospectus supplement shall be underwriters of the securities offered thereby.

We may sell the securities through agents from time to time. The prospectus supplement will name any agent involved in the offer or sale of the securities and any commissions we pay to them. Generally, any agent will be acting on a best efforts basis for the period of its appointment.

We may authorize underwriters, dealers or agents to solicit offers by certain purchasers to purchase the securities from us at the public offering price set forth in the prospectus supplement pursuant to delayed delivery contracts providing for payment and delivery on a specified applicable date in the future. The contracts will be subject only to those conditions set forth in the prospectus supplement, and the prospectus supplement will set forth any commissions we pay for solicitation of these contracts.

Agents and underwriters may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act of 1933, as amended, or to contribution with respect to payments which the agents or underwriters may be required to make in respect thereof. Agents and underwriters may be customers of, engage in transactions with, or perform services for us in the ordinary course of business.

We may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including in short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of securities, and may use securities received from us in settlement of those derivatives to close out any related open borrowings of securities. The third party in such sale transactions will be an underwriter and will be identified in the applicable prospectus supplement (or a post-effective amendment). We may also use underwriters or such other third parties with whom we have a material relationship. We will describe the nature of any such relationship in the applicable prospectus supplement.

### At-the-Market Offerings

Upon written instruction from us, after entering into a distribution agency agreement with us, a sales agent may use its commercially reasonable efforts to sell on our behalf, as our agent, the shares of common stock offered as agreed upon by us and the sales agent. We will designate the maximum amount of shares of common stock to be sold through the sales agent, on a daily basis or otherwise as we and the sales agent agree. Subject to the terms and conditions of the applicable distribution agency agreement, the sales agent will use its commercially reasonable efforts to sell, as our sales agent and on our behalf, all of the designated shares of common stock. We may instruct the sales agent not to sell shares of common stock if the sales cannot be effected at or above the price designated by us in any such instruction. We may suspend the offering of shares of common stock under any distribution agency agreement by notifying the sales agent. Likewise, the sales agent may suspend the offering of shares of common stock under the applicable distribution agency agreement by notifying us of such suspension.

We also may sell shares to the sales agent as principal for its own account at a price agreed upon at the time of sale. If we sell shares to the sales agent as principal, we

will enter into a separate agreement setting forth the terms of such transaction.

It is contemplated that the distribution agreements entered into with sales agents will allow such sales agents to make sales in privately negotiated transactions and/or under any other method permitted by law, including sales deemed to be an "at-the-market" offering as defined in Rule 415 promulgated under the Securities Act, sales made directly on the Nasdaq Capital Market, the existing trading market for our common stock, or sales made to or through a market maker other than on an exchange. The name of any such underwriter or agent involved in the offer and sale of our common stock, the amounts underwritten, and the nature of its obligations to take our common stock will be described in the applicable prospectus supplement.

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#### LEGAL MATTERS

Certain legal matters will be passed upon for us by Alston & Bird LLP, New York, New York. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

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#### EXPERTS

The financial statements of Avenue Therapeutics, Inc. as of December 31, 2020 and 2019 and for each of the two years in the period ended December 31, 2020 incorporated by reference in this Prospectus and in the Registration Statement have been so incorporated in reliance on the report of BDO USA, LLP, an independent registered public accounting firm, incorporated herein by reference, given on the authority of said firm as experts in auditing and accounting. The report on the financial statements contains an explanatory paragraph regarding the Company's ability to continue as a going concern.

#### WHERE YOU CAN FIND MORE INFORMATION

We are a public company and file reports with the SEC on an annual basis using Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K. Additionally, the SEC maintains a website that contains annual, quarterly, and current reports, proxy statements, and other information that issuers (including us) file electronically with the SEC. The SEC's website address is <http://www.sec.gov>. You can also obtain copies of materials we file with the SEC from our Internet website found at [www.avenuetx.com](http://www.avenuetx.com). Our stock is quoted on the Nasdaq Capital Market under the symbol "ATXI". We have not incorporated by reference into this prospectus the information on our website, and you should not consider it to be a part of this prospectus.

#### INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to "incorporate by reference" the information we file with them which means that we can disclose important information to you by referring you to those documents instead of having to repeat the information in this prospectus and accompanying prospectus. The information incorporated by reference is considered to be part of this prospectus and accompanying prospectus, and later information that we file with the SEC will automatically update and supersede this information. This prospectus incorporates by reference the documents listed below and any future filings made with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (1) after the date of the initial registration statement, as amended, and prior to effectiveness of the registration statement, and (2) after the date of this prospectus and prior to the termination of this offering. Such information will automatically update and supersede the information contained in this prospectus and the documents listed below; provided, however, that we are not, unless specifically indicated, incorporating any information furnished under Item 2.02 or Item 7.01 of any current report on Form 8-K, whether listed below or filed in the future, or related exhibits furnished pursuant to Item 9.01 of Form 8-K:

- a) [Our Annual Report on Form 10-K for the year ended December 31, 2020 filed with the SEC on March 31, 2021](#);
- b) Our Quarterly Reports on Form 10-Q for the quarters ended June 30, 2021, filed with the SEC on [August 16, 2021](#), and March 31, 2021, filed with the SEC on [May 17, 2021](#); and
- c) Our Current Reports on Form 8-K filed with the SEC on [January 8, 2021](#), [February 16, 2021](#), [March 1, 2021](#), [April 5, 2021](#), [May 3, 2021](#), [June 14, 2021](#), [July 15, 2021](#), [July 29, 2021](#), [August 27, 2021](#), [September 1, 2021](#), [September 3, 2021](#) and [September 21, 2021](#).

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering, including all such documents we may file with the SEC after the date of the initial registration statement and prior to the effectiveness of the registration statement, but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus and deemed to be part of this prospectus from the date of the filing of such reports and documents.

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[ ] Shares of Common Stock

**AVENUE THERPEAUTICS, INC.**

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PROSPECTUS SUPPLEMENT

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**AEGIS CAPITAL**

November , 2021

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