

PROSPECTUS SUPPLEMENT
To the Prospectus dated December 10, 2021



**448,000 Shares of Common Stock
Pre-Funded Warrants to purchase up to 1,492,299 Shares of Common Stock**

We are offering 448,000 shares of our common stock, par value \$0.0001 per share (“Common Stock”), and pre-funded warrants (“Pre-funded Warrants”) to purchase up to 1,492,299 shares of our Common Stock, directly to a single accredited investor, pursuant to this prospectus supplement and the accompanying prospectus. Each Pre-funded Warrant will have an exercise price of \$0.001 per share and will be exercisable upon issuance until exercised in full, and is subject to adjustment in the event of stock splits, dividends, subsequent rights offerings, pro rata distributions, and certain fundamental transactions, as more fully described in the section of this prospectus titled “Description of Securities We are Offering.” The purchase price of each Pre-funded Warrant is \$1.549, which equals the price per share of Common Stock being sold in this offering.

In a concurrent private placement, we are also selling to the same accredited investor that received shares of Common Stock and Pre-funded Warrants pursuant to this prospectus supplement, warrants (“Warrants”) to purchase up to 1,940,299 shares of Common Stock. The Warrants are being sold for \$0.125 per Warrant, have an exercise price of \$1.55 per share and are exercisable for a period of three (3) years from the date of the issuance. The Warrants, and the shares of Common Stock issuable upon exercise of the Warrants, are being offered pursuant to the exemption provided in Section 4(a)(2) under the Securities Act of 1933, as amended (the “Securities Act”), and Rule 506(b) promulgated thereunder and are not being registered under the Securities Act at this time or offered pursuant to this prospectus supplement and the accompanying prospectus. The Warrants are more fully described in the section of this Prospectus Supplement titled “Private Placement Transaction.”

Our Common Stock is listed on the Nasdaq Capital Market under the symbol “ATXI.” On January 26, 2023, the last trading day before our entry into the securities purchase agreement providing for the sale of the shares of Common Stock and Pre-funded Warrants, the last reported sale price of our Common Stock on the Nasdaq Capital Market was \$1.55 per share. There is no established public trading market for the Pre-funded Warrants being offered in this offering and the Warrants being sold in a concurrent private placement, and we do not expect a market to develop. In addition, we do not intend to apply for listing the Pre-funded Warrants or the Warrants on any national securities exchange or other trading market. Without an active market, the liquidity of the Pre-funded Warrants and the Warrants will be limited.

We have engaged Aegis Capital Corp. (the “Placement Agent”) as our exclusive placement agent in connection with this offering. The Placement Agent has agreed to use its reasonable best efforts to sell the securities offered by this prospectus supplement and the accompanying prospectus. The Placement Agent is not purchasing or selling any shares offered by this prospectus supplement and the accompanying base prospectus. See “Plan of Distribution” beginning on page S-21 of this prospectus supplement for more information regarding these arrangements.

Investing in our securities involves a high degree of risk. See “Risk Factors” beginning on page S-8 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, 2021 and in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2022, 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 securities.

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		
	Per share	Underlying Pre-funded Warrant	Total
Offering price	\$ 1.55	\$ 1.549	\$ 3,007,463.45
Placement agent fees(1)	\$ 0.124	\$ 0.1239	\$ 240,597.08
Proceeds, before expenses, to us(2)	\$ 1.426	\$ 1.4259	\$ 2,766,866.37

- (1) We have agreed to pay the Placement Agent a cash placement commission equal to 8.0% of the aggregate proceeds from the sale of the shares of Common Stock and Pre-funded Warrants sold in this offering. We have also agreed to reimburse the Placement Agent for certain expenses incurred in connection with this offering. See “Plan of Distribution” beginning on page S-21 for additional information regarding the compensation to be paid to the Placement Agent.
- (2) The amount of the offering proceeds to us presented in this table does not take into account the proceeds from our concurrent private placement or the exercise of any of the Warrants being issued in the concurrent private placement.

Delivery of the securities is expected to be made on or about January 31, 2023, subject to the satisfaction of certain closing conditions.

AEGIS CAPITAL CORP.

The date of this prospectus supplement is January 27, 2023.

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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 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 December 10, 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 Placement Agent has 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 securities, you should not rely upon any information other than the information in this prospectus supplement, the accompanying prospectus, or 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 securities 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 titled “*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.

Unless otherwise stated, all references in this prospectus supplement to “we,” “us,” “our,” “Avenue,” the “Company” and similar designations refer to Avenue Therapeutics, Inc. and its consolidated subsidiaries. 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.

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SPECIAL CAUTIONARY NOTICE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement contains predictive or “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. All statements other than statements of current or historical fact contained in this press release, including statements that express our intentions, plans, objectives, beliefs, expectations, strategies, predictions or any other statements relating to our future activities or other future events or conditions are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “will,” “should,” “would” and similar expressions are intended to identify forward-looking statements. These statements are based on current expectations, estimates and projections made by management about our business, our industry and other conditions affecting our financial condition, results of operations or business prospects. These statements are not guarantees of future performance and involve risks, uncertainties and assumptions that are difficult to predict. Therefore, actual outcomes and results may differ materially from what is expressed or forecasted in, or implied by, the forward-looking statements due to numerous risks and uncertainties. Factors that could cause such outcomes and results to differ include, but are not limited to, risks and uncertainties arising from: 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 incurring capital expenditures to expand our research and development and manufacturing capabilities; expectations for generating revenue or becoming profitable on a sustained basis; expectations or ability to enter into marketing and other partnership agreements; 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 products by doctors, patients or payors; our ability to compete against other companies and research institutions; our ability to secure adequate protection for our intellectual property; our ability to attract and retain key personnel; availability of reimbursement for our products; estimates of the sufficiency of our existing cash and cash equivalents and investments to finance our operating requirements, including expectations regarding the value and liquidity of our investments; the volatility of our stock price; expected losses expectations for future capital requirements; uncertainty around the integration of the Baergic Bio, Inc. acquisition; and those risks discussed in our filings which we make with the SEC. Any forward-looking statements speak only as of the date on which they are made, and we undertake no obligation to publicly update or revise any forward-looking statements to reflect events or circumstances that may arise after the date of this prospectus supplement, except as required by applicable law. Investors should evaluate any statements made by us in light of these important factors.

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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;
- expectations for incurring capital expenditures to expand our research and development and manufacturing capabilities;
- 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 marketing and other partnership agreements;
- 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 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 attract and retain key personnel;
- regulatory developments in the United States and foreign countries;
- market conditions in the pharmaceutical and biotechnology sectors;
- estimates of the sufficiency of our existing cash and cash equivalents and investments to finance our operating requirements, including expectations regarding the value and liquidity of our investments;
- the volatility of our stock price;
- expected losses;
- expectations for future capital requirements.
- the ongoing impact of the COVID-19 pandemic; and
- our ability to successfully implement our strategy.

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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-8 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 focused on the development and commercialization of therapies for the treatment of central nervous system diseases. Our lead product candidate is intravenous (IV) Tramadol (“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 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 (the “Second CRL”) from the FDA regarding our NDA for IV Tramadol. 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. On February 15, 2022, we had our Advisory Committee meeting with the FDA. In the final part of the public meeting, the Advisory Committee voted yes or no on the following question: “Has the Applicant submitted adequate information to support the position that the benefits of their product outweigh the risks for the management of acute pain severe enough to require an opioid analgesic in an inpatient setting?” The results were 8 yes votes and 14 no votes. On March 18, 2022, we received an Appeal Denied Letter (the “Letter”) from the OND in response to the FDRR. On August 31, 2022, the Company disclosed that, on June 17, 2022, following the receipt of the Letter, the Company submitted a Type A Meeting Request and related briefing documents to the FDA. The meeting was granted by the Division of Anesthesia, Analgesia, and Addiction Products (“DAAAP”) on June 27, 2022, and scheduled for August 9, 2022. The Company submitted a briefing document presenting a study design that the Company believed has the potential to address the comments and deficiencies noted in the Letter and sought the DAAAP’s guidance to refine the study design that would support a resubmission of a New Drug Application for the Company’s current lead product candidate, intravenous Tramadol. The meeting on August 9, 2022 was a collaborative discussion on the study design and potential path forward. We intend to incorporate the FDA’s suggestions from the meeting minutes and submit a detailed study protocol that could form the basis for the submission of a complete response to the Second CRL. We continue to evaluate next steps with regard to IV Tramadol.

We have recently expanded our business with the acquisition of Baergic Bio, Inc. (“Baergic”) and its asset BAER-101, which strategically aligns with Avenue’s goals of building a central nervous system pipeline. On May 11, 2022, we entered into a stock contribution agreement (the “Contribution Agreement”) with Fortress Biotech, Inc. (“Fortress”) pursuant to which Fortress agreed to transfer ownership of 100% of its shares (common and preferred) in Baergic, then a private subsidiary company of Fortress, to us. The acquisition was completed on November 8, 2022 and Baergic is currently a private, majority owned subsidiary of the Company. Under the Contribution Agreement, Fortress also agreed to assign to us certain intercompany agreements existing between Fortress and Baergic, including a Founders Agreement and Management Services Agreement. Consummation of the transactions contemplated by the Contribution Agreement was subject to the satisfaction of certain conditions precedent, including, inter alia: (i) the closing of an equity financing by the Company resulting in gross proceeds of no less than \$7.5 million, (ii) the agreement by minority Avenue stockholder InvaGen Pharmaceuticals Inc. (“InvaGen”) to (A) have 100% of its shares in us repurchased by us and (B) terminate certain of the agreements into which it entered with us and/or Fortress in connection with InvaGen’s 2019 equity investment in us, which will eliminate certain negative consent rights of InvaGen over us and restore certain rights and privileges of Fortress in us (all upon terms to be agreed upon with InvaGen); and (iii) the sustained listing of our Common Stock on Nasdaq. These conditions were satisfied as of the date of our closing of the acquisition of Baergic.

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RECENT DEVELOPMENTS

October 2022 Public Offering

On October 6, 2022, we entered into an Underwriting Agreement (the “Underwriting Agreement”) with Aegis, as underwriter (the “Underwriter”), related to our underwritten public offering (the “Public Offering”) of 2,652,065 units (“Public Offering Units”) and 984,300 pre-funded units (“Public Offering Pre-funded Units”). Each

Public Offering Unit consisted of one share (“Share”) of Common Stock and one warrant to purchase one share of Common Stock (each, a “Public Offering Warrant” and, collectively, the “Public Offering Warrants”), and each Pre-funded Unit consisted of one pre-funded warrant to purchase one share of Common Stock (each, a “Public Offering Pre-funded Warrant” and collectively, the “Public Offering Pre-funded Warrants”) and one Public Offering Warrant. The Public Offering Units were sold at a price of \$3.30 per Public Offering Unit, and the Public Offering Pre-Funded Units were sold at a price of \$3.2999 (\$3.30 less \$0.0001, the exercise price of the Public Offering Pre-funded Warrants).

The Public Offering Warrants became exercisable upon issuance and are exercisable for a period of five years after the issuance date. The Shares, the Public Offering Pre-funded Warrants and the Public Offering Warrants were immediately separable upon issuance and were issued separately. The Underwriter was granted a 45-day option to purchase up to an aggregate of (i) 545,454 additional Shares and/or Public Offering Pre-funded Units, representing 15% of the Shares and Public Offering Pre-funded Warrants sold in the Public Offering, and/or (ii) Public Offering Warrants to purchase 545,454 additional Shares, representing 15% of the Public Offering Warrants sold in the Public Offering, which it initially exercised, in part, electing to purchase 545,454 Public Offering Warrants at a purchase price of \$0.01 per Warrant. We consummated the transactions contemplated by the Offering and the Underwriting Agreement on October 11, 2022. Prior to the closing date of the Offering, investors in certain of the Public Offering Pre-funded Warrants, pursuant to the terms thereof, elected to exercise 949,900 Public Offering Pre-funded Warrants. Accordingly, at the closing, we issued 949,900 fewer Public Offering Pre-funded Warrants and, in lieu thereof, the corresponding 949,900 shares of Common Stock.

The net proceeds from the Public Offering were approximately \$10.4 million, after deducting underwriting discounts and commissions and estimated offering expenses payable to us.

InvaGen Share Repurchase

In connection with the closing of the Public Offering, on October 11, 2022, the Company consummated the transactions contemplated by the Share Repurchase Agreement with InvaGen, pursuant to which the Company repurchased 100% of the shares in the Company held by InvaGen (the “InvaGen Shares”) for a purchase price of \$3 million. In addition, under the Share Repurchase Agreement the Company agreed to pay InvaGen an additional amount as a contingent fee, payable in the form of seven and a half percent (7.5%) of the proceeds of future financings, up to \$4 million. In connection with the closing of the Share Repurchase Agreement, which occurred on October 31, 2022, all of the rights retained by InvaGen pursuant to the Stockholders Agreement entered into by and among the Company, InvaGen and Fortress on November 12, 2018, were terminated.

CORPORATE INFORMATION

Our principal executive offices are located at 1111 Kane Concourse, Suite 301, Bay Harbor Islands, Florida 33154, and our telephone number is 781-652-4500. We maintain a website on the Internet at www.avenuetx.com and our e-mail address is 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.

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THE OFFERING

Securities offered by us	448,000 shares of Common Stock; and Pre-funded Warrants to purchase 1,492,299 shares of Common Stock
Offering Price	\$1.55 per share of Common Stock and \$1.549 per Pre-funded Warrant
Common Stock to be outstanding after the offering	7,023,200 shares of Common Stock, assuming exercise of all Pre-funded Warrants being offered herein, and no exercise of the Warrants being issued in a concurrent private placement transaction.
Use of Proceeds	<p>We estimate the net proceeds from this offering will be approximately \$2.6 million, after deducting placement agent fees and estimated offering expenses payable by us.</p> <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 candidates to obtain regulatory approval from the FDA. However, we will have broad discretion to allocate the net proceeds of this offering.</p> <p>See “<i>Use of Proceeds</i>” on page S-13 of this prospectus supplement.</p>
Lock-Up	Our directors, officers and the holders of 10% of our outstanding shares of Common Stock have agreed to enter into lock-ups restricting the transfer of shares of or relating to our capital stock for 90 days after the closing of this offering.
Participation Right	We have granted the purchaser in this offering the right to participate in any subsequent offering of securities by us, subject to certain exceptions, by purchasing up to 50% of the securities offered by us in such subsequent financing on the same terms, conditions and price provided for in such transaction.
Concurrent Private Placement	In a concurrent private placement, we are issuing to the same accredited investor purchasing shares of our Common Stock and Pre-funded Warrants in this offering, Warrants to purchase up to 1,940,299 shares of Common Stock at an exercise price of \$1.55 per share, exercisable for a period of three years from the date of issuance. We will receive gross proceeds from the concurrent private placement transaction of approximately \$0.24 million. The Warrants and the shares of Common Stock issuable upon the exercise of the Warrants are not being offered pursuant to this prospectus supplement and the accompanying prospectus and are being offered pursuant to the exemption provided in Section 4(a)(2) under the Securities Act. See “ <i>Private Placement Transaction</i> ” below.
Risk factors	See “ <i>Risk Factors</i> ” beginning on each of page S-8 of this prospectus supplement, beginning on page 3 of the accompanying prospectus and in our Annual Report on Form 10-K for the year ended December 31, 2021, which is incorporated by reference herein, for a discussion of factors that you should consider before investing in our securities.
Nasdaq Capital Market symbol	ATXI

The number of shares of Common Stock to be outstanding after this offering is based on 5,082,901 shares of our Common Stock outstanding as of January 26, 2023, and excludes:

- 4,137,915 shares of Common Stock issuable upon exercise of outstanding warrants having a weighted-average exercise price of \$1.55 per share
- 13,149 shares of Common Stock issuable upon the vesting and settlement of outstanding restricted stock award/units;
- 122,489 shares of Common Stock reserved for issuance and available for future grant under our 2015 Incentive Plan; and
- 1,940,299 shares of Common Stock issuable upon exercise of the Warrants being issued in the concurrent private placement.

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

RISK FACTORS

Investing in our securities 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 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, 2021, 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 Related to this Offering and our Securities

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' securities. 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 Common Stock being offered is substantially higher than the net tangible book value per share of 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 \$0.79 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, as will the exercise of the Pre-funded Warrants, the Warrants sold in our concurrent private placement or other previously outstanding warrants. See the section titled "Dilution" below for a more detailed discussion of the dilution you would incur if you purchase securities in this offering.

The Pre-funded Warrants are not listed for trading on any exchange, so the ability to trade the shares of Pre-funded Warrants is limited.

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

The Pre-funded Warrants are speculative in nature.

Except as otherwise provided in the Pre-funded Warrants and Warrants, until holders of Pre-funded Warrants and Warrants acquire shares of Common Stock upon exercise of the Pre-funded Warrants or Warrants, holders of Pre-funded Warrants and Warrants will have no rights with respect to our Common Stock underlying such Pre-funded Warrants or Warrants. Upon exercise of the Pre-funded Warrants or Warrants, the holders will be entitled to exercise the rights of a shareholder only as to matters for which the record date occurs after the exercise date. Moreover, following this offering, the market value of the Pre-funded Warrants and Warrants is uncertain. There can be no assurance that the market price of our Common Stock will ever equal or exceed the price of the Pre-funded Warrants or Warrants, and, consequently, whether it will ever be profitable for investors to exercise their Pre-funded Warrants or Warrants.

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 Common Stock in the public market could reduce the prevailing market prices for our Common Stock. Substantially all of our outstanding Common Stock is eligible for sale as are shares of 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.

Holders of Pre-funded Warrants will have no rights as common stockholders until such holders exercise their Pre-funded Warrants.

Until holders of Pre-funded Warrants acquire shares of our Common Stock upon exercise thereof, such holders will have no rights with respect to the shares of our Common Stock underlying the Pre-funded Warrants, except to the extent that holders of the Pre-funded Warrants have certain rights to participate in distributions or dividends paid on our Common Stock as set forth in the Pre-funded Warrants. Upon exercise of the Pre-funded Warrants, the holders will be entitled to exercise the rights of a common stockholder only as to matters for which the record date occurs after the exercise date.

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.

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CAPITALIZATION

The following table sets forth our capitalization as of September 30, 2022:

- on an actual basis;
- on a pro forma basis to give effect to the issuance and sale of 3,636,365 shares of Common Stock pursuant to an underwritten public offering that we closed on October 11, 2022, the full exercise of all pre-funded warrants issued in such underwritten public offering, and the repurchase of 388,888 shares of Common Stock by the Company pursuant to a Share Repurchase Agreement that we completed in October 2022; and
- on a pro forma as adjusted basis to give further effect to the issuance and sale of (a) 448,000 shares of Common Stock at an offering price of \$1.55 and (b) Pre-funded Warrants to purchase up to 1,492,299 shares of Common Stock at an offering price of \$1.549 per Pre-funded Warrant, after deducting placement agent fees 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 each of our Annual Report on Form 10-K for the year ended December 31, 2021 and our Quarterly Report on Form 10-Q for the quarter ended September 30, 2022.

(\$ in thousands, except share and per share amounts)	September 30, 2022 (unaudited)		
	Actual	Pro Forma	As Adjusted
Cash and cash equivalents	\$ 217	\$ 7,630	\$ 10,252
Stockholders’ Equity (Deficit)			
Preferred Stock (\$0.0001 par value), 2,000,000 shares authorized			
Class A Preferred Stock, 250,000 shares issued and outstanding	—	—	—
Common Stock (\$0.0001 par value), 20,000,000 shares authorized			
Common shares, 1,475,652 shares issued and outstanding; 4,723,129 pro forma, and 6,663,428 pro forma as adjusted	—	—	1
Additional paid-in capital	81,087	91,500	94,506
Accumulated deficit	(81,126)	(81,126)	(81,126)
Total Stockholders’ Equity (Deficit)	(39)	10,374	13,381
Total Capitalization	\$ (39)	\$ 10,374	13,381

The number of shares of Common Stock to be outstanding after this offering is based on 1,475,652 shares of our Common Stock outstanding as of September 30, 2022, and excludes:

- 4,182,815 shares of Common Stock issuable upon exercise of outstanding warrants having a weighted-average exercise price of \$1.55 per share
- 13,149 shares of Common Stock issuable upon the vesting and settlement of outstanding restricted stock award/units;
- 122,489 shares of Common Stock reserved for issuance and available for future grant under our 2015 Incentive Plan;
- 322,225 shares of Common Stock issuable to Fortress Biotech, Inc. pursuant to the Founder’s Agreement equity fee from the offering closed October 11, 2022, and Class A Preferred Stock annual dividend paid to Fortress Biotech, Inc. on January 3, 2023; and
- 1,940,299 shares of Common Stock issuable upon exercise of the warrants acquired as part of the offering closed on January 31, 2023.

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 of Common Stock or Pre-funded Warrants offered by this prospectus supplement and the accompanying prospectus will suffer immediate and substantial dilution in the net tangible book value per share of Common Stock or Pre-funded Warrant 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 Common Stock outstanding as of September 30, 2022. Our net tangible book value as of September 30, 2022 was approximately \$(39) thousand, or \$(0.03) per share of 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 offering price of \$1.55 per share and the sale of Pre-funded Warrants to purchase 1,492,299 shares of Common Stock for \$1.549 per share, and after deducting the fees of the placement agent and the estimated expenses payable by us, our net tangible book value as of September 30, 2022 would have been approximately \$(39) thousand million, or \$(0.03) per share of Common Stock. This represents an immediate increase in net book value of \$0.76 per share to our existing stockholders and an immediate dilution in net tangible book value of \$0.79 per share to new investors participating in this offering.

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

Offering price per share	\$	1.55
Net tangible book value per share as of September 30, 2022	\$	(0.03)
Increase per share attributable to the offering	\$	0.79
As-adjusted net tangible book value per share after giving effect to the offering	\$	0.76
Dilution in net tangible book value per share to new investors	\$	0.79

The foregoing discussion and table do not take into account further dilution to new investors that could occur upon the exercise of outstanding warrants or pre-funded warrants having a per share exercise or conversion price less than the per share offering price to the public in this offering, and do not take into account the effects of our public offering of common stock, pre-funded warrants and warrants in October 2022.

The number of shares of Common Stock to be outstanding after this offering is based on 1,475,652 shares of Common Stock outstanding as of September 30, 2022, and excludes:

- 3,636,365 shares of Common Stock issued pursuant to an underwritten public offering we closed on October 11, 2022;
- 388,888 shares of Common Stock repurchased by the Company pursuant to a Share Repurchase Agreement in October 2022;
- 4,182,815 shares of Common Stock issuable upon exercise of outstanding warrants having a weighted-average exercise price of \$1.55 per share;
- 13,149 shares of Common Stock issuable upon the vesting and settlement of outstanding restricted stock award/units;
- 122,489 shares of Common Stock reserved for issuance and available for future grant under our 2015 Incentive Plan;
- 322,225 shares of Common Stock issuable to Fortress Biotech, Inc. pursuant to the Founder's Agreement equity fee from the offering closed October 11, 2022, and Class A Preferred Stock annual dividend paid to Fortress Biotech, Inc. on January 3, 2023; and
- 1,940,299 shares of Common Stock issuable upon exercise of the warrants acquired as part of the offering closed on January 31, 2023.

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.

To the extent any of these outstanding options or warrants are exercised at a price less than the public offering price, there may be further dilution to purchasers of our Common Stock in this offering.

The information above assumes no exercise of Warrants.

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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 \$2.6 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 the particular uses for the net proceeds to us from an offering. Accordingly, our management will have broad discretion in the application of proceeds.

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DESCRIPTION OF THE SECURITIES WE ARE OFFERING

We are offering through this prospectus supplement and the accompanying prospectus (i) 448,000 shares of our Common Stock, and (ii) Pre-funded Warrants to purchase up to 1,492,299 shares of our Common Stock. We are also registering the offer and sale of shares of our Common Stock issuable from time to time upon exercise of the Pre-funded Warrants offered hereby.

Authorized Capital Stock

Our authorized capital stock consists of 20,000,000 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 January 26, 2023, there were 5,082,901 shares of our Common Stock outstanding held by approximately 36 record stockholders.

Common Stock

Voting Rights

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, including shares of our outstanding Class A Preferred Stock, each of which as the voting power of 1.1 times (A) the shares of outstanding common stock plus (B) the whole shares of common stock into which the shares of outstanding the Class A Preferred Stock are convertible, divided by the number of shares of outstanding Class A Preferred Stock.

Liquidation and Other Rights

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.

Listing

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.

Dividends

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. Pursuant to the certificate of designation relating to the series A preferred stock, we are prohibited from paying dividends on our Common Stock until all dividends required to be paid to the holders of our Class A Preferred Stock have been paid or declared and set apart for payment.

Anti-Takeover Effects of Various Provisions of Delaware Law and Avenue's Certificate of Incorporation and By-Laws

Provisions of the General Corporation Law of the State of Delaware, as amended (the "DGCL") and our Third Amended and Restated Certificate of Incorporation, as amended (the "Certificate of Incorporation") and Amended and Restated By-Laws, as amended (the "By-Laws") could make it more difficult to acquire Avenue by means of a tender offer, a proxy contest or otherwise, or to remove incumbent officers and directors. These provisions, including those summarized below, may encourage certain types of coercive takeover practices and takeover bids.

Delaware Anti-Takeover Statute. In general, Section 203 of the DGCL prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a period of three years following the time the person became an interested stockholder, unless the business combination or the acquisition of shares that resulted in a stockholder becoming an interested stockholder is approved in a prescribed manner. Generally, a "business combination" includes a merger, asset or stock sale or other transaction resulting in a financial benefit to the interested stockholder. Generally, an "interested stockholder" is a person who, together with affiliates and associates, owns (or within three years prior to the determination of interested stockholder status did own) 15% or more of a corporation's voting stock. However, our Certificate of Incorporation provides that we are not subject to the anti-takeover provisions of Section 203 of the DGCL.

Removal. Subject to the rights of any holders of any outstanding series of our Preferred Stock, stockholders may remove our directors with or without cause. Removal will require the affirmative vote of holders of a majority of our voting stock.

Size of Board and Vacancies. Our By-Laws provide that the number of directors be fixed exclusively by the board of directors. Any vacancies created on its board of directors resulting from any increase in the authorized number of directors or the death, resignation, retirement, disqualification, removal from office or other cause will be filled by a majority of the board of directors then in office, even if less than a quorum is present, or by a sole remaining director. Any director appointed to fill a vacancy on our board of directors will be appointed until the next annual meeting and until his or her successor has been elected and qualified.

Requirements for Advance Notification of Stockholder Nominations and Proposals. Our By-Laws establish advance notice procedures with respect to stockholder proposals and nomination of candidates for election as directors other than nominations made by or at the direction of its board of directors or a committee of our board of directors.

Undesignated Preferred Stock. Our board of directors is authorized to issue up to 2,000,000 shares of preferred stock without additional stockholder approval, which preferred stock could have voting rights or conversion rights that, if exercised, could adversely affect the voting power of the holders of Common Stock. The issuance of shares of preferred stock may have the effect of delaying, deferring or preventing a change in control of the Company without any action by the Company's stockholders.

Limitation on Liability of Directors and Indemnification of Directors and Officers

Elimination of Liability of Directors. The DGCL authorizes corporations to limit or eliminate the personal liability of directors to corporations and their stockholders for monetary damages for breaches of directors' fiduciary duties as directors, and our Certificate of Incorporation includes such an exculpation provision. Our Certificate of Incorporation provides that, to the fullest extent permitted by the DGCL, no director will be personally liable to us or to our stockholders for monetary damages for breach of fiduciary duty as a director. While our Certificate of Incorporation provides directors with protection from awards for monetary damages for breaches of their duty of care, it does not eliminate this duty. Accordingly, our Certificate of Incorporation has no effect on the availability of equitable remedies such as an injunction or rescission based on a director's breach of his or her duty of care. The provisions apply to an officer of Avenue only if he or she is a director of Avenue and is acting in his or her capacity as director, and do not apply to officers of Avenue who are not directors. Additionally, our Certificate of Incorporation provides that, to the fullest extent permitted by law, we renounce any interest or expectancy in a transaction or matter that may be a corporate opportunity for us if it was presented to, or acquired, created or developed by, or which otherwise comes into the possession of, (i) any director on our board of directors who is not an employee of the Company or any of its subsidiaries, or (ii) any holder of our Class A Preferred Stock or any affiliate or other related person of any such holder, other than someone who is an employee of the Company or any of its subsidiaries, and no person shall have any duty to present such corporate opportunity to us and will not be liable to us for pursuing or acquiring such opportunity, or referring such opportunity to a third party.

Indemnification of Directors, Officers and Employees. Our By-Laws require us to indemnify any person who was or is a party or is threatened to be made a party to, or was otherwise involved in, a legal proceeding by reason of the fact that he or she is or was a director, officer or employee of Avenue or, while a director, officer or employee of Avenue, is or was serving in a fiduciary capacity with another enterprise (including any corporation, partnership, limited liability company, joint venture, trust, association or other unincorporated organization or other entity and any employee benefit plan, to the fullest extent authorized by the DGCL, as it exists or may be amended, against all expense, liability and loss (including attorneys' fees, judgments, fines, U.S. Employee Retirement Income Security Act of 1974, as amended, excise taxes or penalties and amounts paid in settlement by or on behalf of such person) actually and reasonably incurred in connection with such service. We are authorized under our By-Laws to carry directors' and officers' insurance protecting us, any director, officer or employee of ours or, against any expense, liability or loss, whether or not we have the power to indemnify the person under the DGCL. We may, to the extent authorized from time to time, indemnify any of our agents to the fullest extent permitted with respect to directors, officers and employees in our By-Laws.

The limitation of liability and indemnification provisions in our Certificate of Incorporation and By-Laws may discourage stockholders from bringing a lawsuit against our directors for breach of fiduciary duty. These provisions also may reduce the likelihood of derivative litigation against our directors and officers, even though such an action, if successful, might otherwise benefit us and our stockholders. By its terms, the indemnification provided for in our By-Laws is not exclusive of any other rights that the indemnified party may be or become entitled to under any law, agreement, vote of stockholders or directors, provisions of our Certificate of Incorporation or By-Laws or otherwise. Any amendment, alteration or repeal of our By-Laws' indemnification provisions is, by the terms of our By-Laws, prospective only and will not adversely affect the rights of any indemnity in effect at the time of any act or omission occurring prior to such amendment, alteration or repeal.

Pre-funded Warrants issued in this Offering

The following summary of certain terms and provisions of the Pre-funded Warrants being offered in this offering is not complete and is subject to, and qualified in its entirety by the provisions of the form of Pre-funded Warrant, the form of which will be filed with the SEC as an exhibit to a Current Report on Form 8-K in connection with this offering and the concurrent private placement and incorporated by reference into the registration statement of which this prospectus supplement and the accompanying prospectus form a part.

Exercisability

The Pre-funded Warrants will be exercisable immediately and may be exercised at any time until the Pre-funded Warrants are exercised in full. The Pre-funded Warrants will be exercisable, at the option of each holder, in whole or in part by delivering to us a duly executed exercise notice and, at any time a registration statement registering the offer and sale of the shares of Common Stock underlying the Pre-funded Warrants under the Securities Act is effective and available for the issuance of such shares, or an exemption from registration under the Securities Act is available for the issuance of such shares, by payment in full of the exercise price of \$0.001 per share in immediately available funds for the number of shares of Common Stock purchased upon such exercise. Alternatively, the holder may elect to exercise the Pre-funded Warrants through a cashless exercise, in which case the holder would receive upon such exercise the net number of shares of Common Stock determined according to the formula set forth in the Pre-funded Warrant. No fractional shares of Common Stock will be issued in connection with the exercise of a Pre-funded Warrant. In lieu of fractional shares, we will, at its option, either pay the holder an amount in cash equal to the fractional amount multiplied by the exercise price or round up to the next whole share.

Exercise Limitation

A holder will not have the right to exercise any portion of the Pre-funded Warrant if the holder (together with its affiliates and certain related parties) would beneficially own in excess of 4.99% of the number of shares of our Common Stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of the Pre-funded Warrants. However, any holder may increase or decrease such percentage to any other percentage not in excess of 9.99%, provided that any increase in such percentage shall not be effective until 61 days following notice from the holder to us.

Exercise Price

The exercise price per whole share of Common Stock purchasable upon exercise of the Pre-funded Warrants is \$0.001. The exercise price is subject to appropriate adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting our Common Stock and also upon any distributions of assets, including cash, stock or other property to our stockholders.

Transferability

Subject to applicable laws, the Pre-funded Warrants may be offered for sale, sold, transferred or assigned without our consent.

Exchange Listing

We do not intend to list the Pre-funded Warrants on any securities exchange or nationally recognized trading system.

Fundamental Transactions

In the event of a fundamental transaction, as described in the Pre-funded Warrants and generally including any reorganization, recapitalization or reclassification of our Common Stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of more than 50% of our outstanding Common Stock, or any person or group becoming the beneficial owner of 50% of the voting power represented by our outstanding Common Stock, the holders of the Pre-funded Warrants will be entitled to receive upon exercise of the Pre-funded Warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the Pre-funded Warrants immediately prior to such fundamental transaction.

Rights as a Stockholder

Except as otherwise provided in the Pre-funded Warrants or by virtue of such holder's ownership of shares of our Common Stock, the holder of a Pre-funded Warrant does not have the rights or privileges of a holder of our Common Stock, including any voting rights, until the holder exercises the Pre-funded Warrant.

Governing Law

The Pre-funded Warrants are governed by New York law.

PRIVATE PLACEMENT TRANSACTION

Concurrently with the sale of Common Stock and Pre-funded Warrants in this offering, we are also offering and selling to the same single accredited investor in this offering Warrants to purchase a share of Common Stock at an exercise price equal to \$1.55 per share (subject to standard adjustments for stock splits, stock dividend, rights offerings, pro rata distributions and certain anti-dilution adjustment rights). We will receive gross proceeds from the concurrent private placement transaction of approximately

\$0.24 million. The Warrants will be exercisable immediately following the date of issuance and expire three (3) years from the date of issuance.

The offer and sale of the Warrants and the Common Stock issuable upon the exercise of such Warrants are not being registered under the Securities Act, such securities are not being offered pursuant to this prospectus supplement and the accompanying prospectus and such securities are instead being offered pursuant to the exemption provided in Section 4(a)(2) under the Securities Act and/or Rule 506(b) promulgated thereunder. Accordingly, the purchaser may only resell shares of Common Stock issued upon exercise of the Warrants pursuant to an effective registration statement under the Securities Act covering the resale of those shares, an exemption under Rule 144 under the Securities Act or another applicable exemption under the Securities Act.

The summary below is not complete and is subject to, and qualified in its entirety by, the provisions of the Warrants, the form of which will be filed with the SEC as an exhibit to a Current Report on Form 8-K in connection with this offering and the concurrent private placement and incorporated by reference into the registration statement of which this prospectus supplement and the accompanying prospectus form a part.

Warrants

The following summary of certain terms and provisions of the Warrants is not complete and is subject to, and qualified in its entirety by the provisions of the Warrant, the form of which will be filed with the SEC as an exhibit to a Current Report on Form 8-K in connection with this offering and the concurrent private placement and incorporated by reference into the registration statement of which this prospectus supplement and the accompanying prospectus form a part.

Exercisability

The Warrants are exercisable immediately and at any time up to the date that is three (3) years after their original issuance. The Warrants will be exercisable, at the option of each holder, in whole or in part by delivering to us a duly executed exercise notice and, at any time a registration statement registering the offer and sale of the shares of Common Stock underlying the Warrants under the Securities Act is effective and available for the issuance of such shares, or an exemption from registration under the Securities Act is available for the issuance of such shares, by payment in full in immediately available funds for the number of shares of Common Stock purchased upon such exercise. If a registration statement registering the offer and sale of the shares of Common Stock underlying the Warrants under the Securities Act is not effective or available and an exemption from registration under the Securities Act is not available for the issuance of such shares, the holder may elect to exercise the Warrant through a cashless exercise, in which case the holder would receive upon such exercise the net number of shares of Common Stock determined according to the formula set forth in the Warrant. No fractional shares of Common Stock will be issued in connection with the exercise of a Warrant. In lieu of fractional shares, we will pay the holder an amount in cash equal to the fractional amount multiplied by the exercise price.

Exercise Limitation

A holder will not have the right to exercise any portion of the Warrant if the holder (together with its affiliates and certain related parties) would beneficially own in excess of 4.99% of the number of shares of our Common Stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of the Warrants. However, any holder may increase or decrease such percentage to any other percentage not in excess of 9.99%, provided that any increase in such percentage shall not be effective until 61 days following notice from the holder to us.

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Exercise Price

The exercise price per whole share of Common Stock purchasable upon exercise of the Warrants is equal to \$1.55. The exercise price is subject to appropriate adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting our Common Stock and also upon any distributions of assets, including cash, stock or other property to our stockholders.

Transferability

Subject to applicable laws, the warrants may be offered for sale, sold, transferred or assigned without our consent.

Exchange Listing

We do not intend to list the Warrants on any securities exchange or nationally recognized trading system.

Fundamental Transactions

In the event of a fundamental transaction, as described in the Warrants and generally including any reorganization, recapitalization or reclassification of our Common Stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of more than 50% of our outstanding Common Stock, or any person or group becoming the beneficial owner of 50% of the voting power represented by our outstanding Common Stock, the holders of the Warrants will be entitled to receive upon exercise of the Warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the Warrants immediately prior to such fundamental transaction.

Rights as a Stockholder

Except as otherwise provided in the Warrants or by virtue of such holder's ownership of shares of our Common Stock, the holder of a Warrant does not have the rights or privileges of a holder of our Common Stock, including any voting rights, until the holder exercises the Warrant.

Governing Law

The Warrants are governed by New York law.

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PLAN OF DISTRIBUTION

Aegis Capital Corp. (the "Placement Agent" or "Aegis") has agreed to act as the exclusive placement agent in connection with this offering subject to the terms and conditions of the placement agency agreement dated January 27, 2023 (the "Placement Agency Agreement"). The Placement Agent is not purchasing or selling any of the securities offered by this prospectus supplement, nor is it required to arrange the purchase or sale of any specific number or dollar amount of securities, but has agreed to use its

reasonable best efforts to arrange for the sale of all of the securities offered hereby. In connection with the offering of the securities described in this prospectus supplement, we have entered into a securities purchase agreement, directly with a single accredited investor in connection with this offering for the sale of all of the securities offered hereby (and the issuance of the Warrants, which are not being offered herein, but are being issued in a separate concurrent offering, exempt from registration under the Securities Act).

We expect to deliver the shares and Pre-funded Warrants being offered pursuant to this prospectus supplement on or about January 31, 2023.

We have agreed to indemnify the Placement Agent against specified liabilities, including liabilities under the Securities Act, and to contribute to payments the Placement Agent may be required to make in respect thereof.

Fees and Expenses

We have agreed to pay the Placement Agent a fee equal to eight percent (8.0%) of the gross proceeds raised in this offering. In addition, we agree to reimburse Aegis for certain of its expenses, including its reasonable fees and expenses of counsel, in an amount up to \$75,000. We have also agreed to pay a non-accountable expense allowance to the Placement Agent in an amount equal to 1% of the gross proceeds raised in this offering and to pay the placement agent a warrant solicitation fee of 5% of the gross proceeds from any exercise of the warrants issued in the concurrent private placement.

The following table shows the per share and total placement agent fees we will pay to the Placement Agent in connection with the sale of Common Stock and Pre-funded Warrants pursuant to this prospectus supplement and the accompanying prospectus assuming the purchase of all shares of Common Stock and Pre-funded Warrants offered hereby. Aegis is also acting as the placement agent for the private placement transaction and is being paid a fee related to the placement of the Warrants.

	Per Share	Per Pre-funded Warrant		Total
Offering price	\$ 1.55	\$ 1.549	\$ 1.549	\$ 3,007,463.45
Placement agent fees	\$ 0.124	\$ 0.1239	\$ 0.1239	\$ 240,597.08
Non-accountable expense allowance	\$ 0.0155	\$ 0.0155	\$ 0.0155	\$ 30,074.63
Proceeds to us, before expenses	\$ 1.4105	\$ 1.4096	\$ 1.4096	\$ 2,736,791.74

After deducting certain fees and expenses due to placement agent and our estimated offering expenses, we expect the net proceeds from this offering to be approximately \$2.6 million.

The Placement Agent may be deemed to be an underwriter within the meaning of Section 2(a)(11) of the Securities Act, and any commissions received by it and any profit realized on the resale of the shares sold by it while acting as principal might be deemed to be underwriting discounts or commissions under the Securities Act. As an underwriter, the Placement Agent would be required to comply with the requirements of the Securities Act and the Securities Exchange Act of 1934, as amended (the "Exchange Act"), including, without limitation, Rule 415(a)(4) under the Securities Act and Rule 10b-5 and Regulation M under the Exchange Act. These rules and regulations may limit the timing of purchases and sales of shares by the Placement Agent acting as principal. Under these rules and regulations, the Placement Agent:

- may not engage in any stabilization activity in connection with our securities; and
- may not bid for or purchase any of our securities or attempt to induce any person to purchase any of our securities, other than as permitted under the Exchange Act, until it has completed its participation in the distribution.

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This prospectus supplement and the accompanying prospectus may be made available in electronic format on websites or through other online services maintained by the Placement Agent or by an affiliate of the Placement Agent. Other than this prospectus supplement and the accompanying prospectus, the information on the Placement Agent's website and any information contained in any other website maintained by the Placement Agent is not part of this prospectus supplement and the accompanying prospectus or the registration statement of which this prospectus supplement and the accompanying prospectus form a part, has not been approved and/or endorsed by us or the Placement Agent, and should not be relied upon by investors.

The foregoing does not purport to be a complete statement of the terms and conditions of the Placement Agency Agreement and the securities purchase agreement. A copy of the securities purchase agreement with the purchasers will be included as an exhibit to our Current Report on Form 8-K to be filed with the SEC in connection with this offering and the concurrent private placement and incorporated by reference into the registration statement of which this prospectus supplement and the accompanying prospectus form a part. See "Incorporation of Certain Information by Reference" and "Where You Can Find More Information."

Right of First Refusal

The Placement Agent shall have a right of first refusal, subject to certain exceptions, to act as sole book-running manager for any and all future public or private equity, equity-linked and debt offerings of the Company or any successor until six (6) months after the closing date of the offering.

Lock-Up Agreements

Pursuant to certain "lock-up" agreements, (a) our directors, executive officers, employees and stockholders holding at least ten percent (10%) of our outstanding shares of common stock 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 Placement Agent for a period of 90 days from the date of effectiveness of this offering, and (b) we, and any successor, have agreed to not, subject to certain exceptions, for a period of three (3) months from the date of this prospectus supplement (1) offer, sell, issue or otherwise transfer or dispose of, directly or indirectly, any equity of the Company, (2) file or cause to be filed any registration with the SEC relating to the placement of any shares of Common Stock of the Company or any securities convertible into or exercisable or exchangeable for shares of Common Stock of the Company, or (3) enter into any agreement or announce the intention to effect any of the actions described in subsections (1) or (2). We have further agreed to not, subject to certain exceptions, for a period of six (6) months from the date of this prospectus supplement, engage in any variable rate transactions (as defined in the purchase agreement).

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.

Other Relationships

The Placement Agent and certain of its 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 supplement, we have no present arrangements with the Placement Agent or any of its affiliates.

Transfer Agent and Registrar

The transfer agent and registrar for our common share is VStock Transfer, LLC.

Listing

Our Common Stock is traded on the Nasdaq Capital Market under the symbol "ATXI."

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LEGAL MATTERS

McGuireWoods LLP, Charlotte, North Carolina, will pass upon the validity of the securities we are offering by this prospectus supplement and the accompanying prospectus. The Placement Agent is 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, 2021 and 2020 and for each of the two years in the period ended December 31, 2021 incorporated by reference in this prospectus supplement and the accompanying prospectus 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. 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(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 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, 2021 filed with the SEC on [March 25, 2022](#);
- b) Our Quarterly Reports on Form 10-Q for the quarters ended September 30, 2022, filed with the SEC on [November 10, 2022](#), June 30, 2022, filed with the SEC on [August 15, 2022](#), and March 31, 2021, filed with the SEC on [May 16, 2022](#); and
- c) Our Current Reports on Form 8-K filed with the SEC on [January 7, 2022](#), [February 11, 2022](#), [February 16, 2022](#), [March 8, 2022](#), [March 21, 2022](#), [March 30, 2022](#), [April 5, 2022](#), [May 13, 2022](#), [May 16, 2022](#), [May 25, 2022](#), [July 29, 2022](#), [August 3, 2022](#), [August 12, 2022](#), [August 31, 2022](#), [September 22, 2022](#), [September 30, 2022](#), [October 12, 2022](#), [October 18, 2022](#), [November 4, 2022](#), [November 8, 2022](#), and [January 25, 2023](#).

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

\$30,000,000



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 \$30,000,000; however, as of the date of this prospectus, under the limitations described below, we are currently only eligible to sell approximately \$2,300,000 of securities. 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 December 3, 2021, the per share closing price of our common stock as reported on the Nasdaq Capital Market was \$1.31 per share.

The aggregate market value of our outstanding common stock held by non-affiliates is approximately \$16,000,000, which was calculated in accordance with General Instruction I.B.6 of Form S-3, based on 18,992,498 shares of common stock outstanding, of which 9,017,340 are held by non-affiliates, at the closing share price of \$1.78 on November 5, 2021, which was the highest closing price of our common stock reported on the NASDAQ Capital Market within the last 60 days prior to the date of this filing.

In this prospectus we are offering up to \$30,000,000 of securities; however, pursuant to General Instruction I.B.6 of Form S-3, in no event will we sell the securities described in this prospectus in a public primary offering with a value exceeding more than one-third of the aggregate market value of our common stock held by non-affiliates in the twelve month period prior to the date of the sale of any such securities, so long as the aggregate market value of our outstanding common stock held by non-affiliates remains below \$75.0 million. As of the date of this prospectus, under such rules and including our prior sales within the twelve month period, we are only eligible to sell up to approximately \$2,300,000, of securities, until our circumstances, as described, change.

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 September 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 December 10, 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 (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. A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee is tentatively scheduled for February 15, 2022. 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 was conditioned upon, among other things, FDA 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 (but would instead retain an option to complete the Merger Transaction up until such time as the SPMA was terminated). Pursuant to the SPMA, we could choose to terminate the SPMA after October 31, 2021, if FDA approval of IV Tramadol had not occurred by such time. On November 1, 2021, we terminated the SPMA.

Even though the SPMA has been terminated, InvaGen retains certain rights pursuant to the Stockholders Agreement, entered into on November 12, 2018 between us, InvaGen and Fortress, and other agreements entered into in connection therewith on such date. 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 us from certain equity issuances and changes to our capital stock without obtaining InvaGen's prior written consent.

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 and our e-mail address is 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").

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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.

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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

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 December 3, 2021, there were 18,992,498 shares of our common stock outstanding held by 38 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.

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 December 3, 2021, there were 14,951 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.

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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. 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 September 30, 2021, filed with the SEC on [November 15, 2021](#), 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](#), [November 4, 2021](#), and [November 10, 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.



**448,000 Shares of Common Stock
Pre-funded Warrants to purchase up to 1,492,299 Shares of Common Stock**

AVENUE THERPEAUTICS, INC.

PROSPECTUS SUPPLEMENT

AEGIS CAPITAL CORP.

January 27, 2023
