

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form S-1

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

Avenue Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware
(State or Other Jurisdiction of
Incorporation or Organization)

2834
(Primary Standard Industrial
Classification Code Number)

47-4113275
(I.R.S. Employer
Identification Number)

**1111 Kane Concourse, Suite 301
Bay Harbor Islands, Florida 33154
(781) 652-4500**

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

**Alexandra MacLean, M.D.
Chief Executive Officer
1111 Kane Concourse, Suite 301
Bay Harbor Islands, Florida 33154
(781) 652-4500**

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

Copies to:

**Rakesh Gopalan
David S. Wolpa
McGuireWoods LLP
201 N. Tryon Street, Suite 3000
Charlotte, NC 28226**

Approximate date of commencement of proposed sale to the public: From time to time after this registration statement becomes effective. If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933 check the following box:

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

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

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

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

| | | | |
|-------------------------|-------------------------------------|---------------------------|-------------------------------------|
| Large accelerated filer | <input type="checkbox"/> | Accelerated filer | <input type="checkbox"/> |
| Non-accelerated filer | <input checked="" type="checkbox"/> | Smaller reporting company | <input checked="" type="checkbox"/> |
| | | Emerging growth company | <input type="checkbox"/> |

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

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

The information in this preliminary prospectus is not complete and may be changed. These securities may not be sold until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities and is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED APRIL 10, 2023



1,940,299 Shares of Common Stock

This prospectus relates to the resale by the selling stockholder (the "Selling Stockholder") identified in this prospectus under the section "*The Selling Stockholder*," or its pledgees, donees, transferees or other successors in interest, from time to time, of up to 1,940,299 shares of our Common Stock, par value \$0.0001 per share (the "Common Stock"), issuable upon the exercise of certain warrants held by the Selling Stockholder (including shares that may be issued to the holder in lieu of fractional shares). We are registering the offer and sale of Common Stock on behalf of the Selling Stockholder to satisfy certain registration rights that we have granted to the Selling Stockholder.

The Selling Stockholder may resell or dispose of the Common Stock, or interests therein, at fixed prices, at prevailing market prices at the time of sale or at prices negotiated with purchasers, to or through underwriters, broker-dealers, agents, or through any other means described in the section of this prospectus titled "*Plan of Distribution*." The Selling Stockholder will bear commissions and discounts, if any, attributable to the sale or disposition of the Common Stock, or interests therein, held by the Selling Stockholder. We will bear all costs, expenses and fees in connection with the registration of the offer and sale of the Common Stock under the Securities Act of 1933, as amended (the "Securities Act"). We will not receive any of the proceeds from the sale of the Common Stock by the Selling Stockholder.

The Common Stock is listed on The Nasdaq Capital Market under the symbol "ATXI." On April 6, 2023, the last reported sale price of our Common Stock was \$1.24 per share. You are urged to obtain current market quotations for our Common Stock.

Investing in our securities involves risks. You should review carefully the risks and uncertainties described under the heading "*Risk Factors*" contained in this prospectus and under similar headings in the other documents that are incorporated by reference into this prospectus, as described on page 8 of this prospectus.

Neither the Securities and Exchange Commission (the "SEC") 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 _____, 2023.

TABLE OF CONTENTS

| | Page |
|--|--------------------|
| ABOUT THIS PROSPECTUS | 1 |
| PROSPECTUS SUMMARY | 6 |
| THE OFFERING | 7 |
| CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS | 8 |
| MARKET AND INDUSTRY DATA AND FORECASTS | 8 |
| RISK FACTORS | 8 |
| DIVIDEND POLICY | 8 |
| USE OF PROCEEDS | 9 |
| DETERMINATION OF OFFERING PRICE | 9 |
| THE SELLING STOCKHOLDER | 10 |
| PLAN OF DISTRIBUTION | 11 |
| DESCRIPTION OF SECURITIES TO BE REGISTERED | 13 |
| MATERIAL UNITED STATES FEDERAL INCOME TAX CONSIDERATIONS | 17 |
| LEGAL MATTERS | 23 |
| EXPERTS | 23 |
| WHERE YOU CAN FIND MORE INFORMATION | 24 |
| INCORPORATION OF CERTAIN INFORMATION BY REFERENCE | 24 |

ABOUT THIS PROSPECTUS

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

This prospectus and the documents incorporated by reference into this prospectus include important information about us, the securities being offered and other information you should know before investing in our securities. You should not assume that the information contained in this prospectus is accurate on any date subsequent to the date set forth on the front cover of this prospectus or that any information we have incorporated by reference is correct on any date subsequent to the date of the document incorporated by reference, even though this prospectus is delivered or securities are sold or otherwise disposed of on a later date. It is important for you to read and consider all information contained in this prospectus, including the documents incorporated by reference therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you under "*Where You Can Find More Information*" and "*Incorporation of Certain Information by Reference*" in this prospectus.

You should rely only on this prospectus and the information incorporated or deemed to be incorporated by reference in this prospectus. We have not authorized anyone to give any information or to make any representation to you other than those contained or incorporated by reference in this prospectus. If anyone provides you with different or inconsistent information, you should not rely on it. This prospectus does not constitute an offer to sell or the solicitation of an offer to buy securities in any jurisdiction to any

person to whom it is unlawful to make such offer or solicitation in such jurisdiction.

Unless otherwise indicated, information contained or incorporated by reference in this prospectus concerning our industry, including our general expectations and market opportunity, is based on information from our own management estimates and research, as well as from industry and general publications and research, surveys and studies conducted by third parties. Management estimates are derived from publicly available information, our knowledge of our industry and assumptions based on such information and knowledge, which we believe to be reasonable. In addition, assumptions and estimates of our and our industry's future performance are necessarily uncertain due to a variety of factors, including those described in section of this prospectus titled "Risk Factors." These and other factors could cause our future performance to differ materially from our assumptions and estimates.

For investors outside the United States: we have not done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of our securities and the distribution of this prospectus outside the United States.

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

This prospectus contains references to trademarks, trade names and service marks belonging to other entities. Solely for convenience, trademarks, trade names and service marks referred to in this prospectus may appear without the ® or TM symbols, but such references are not intended to indicate, in any way, that the applicable licensor will not assert, to the fullest extent under applicable law, its rights to these trademarks and trade names. We do not intend our use or display of other entities' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, any other entities.

PROSPECTUS SUMMARY

This summary highlights selected information from this prospectus and does not contain all of the information that may be important to you in making an investment decision. This summary is qualified in its entirety by the more detailed information included elsewhere in this prospectus and/or incorporated by reference herein. Before making your investment decision with respect to our securities, you should carefully read this entire prospectus, including the information in our filings with the SEC incorporated by reference into this prospectus.

References in this prospectus to the "Company," "we," "us," "our" and similar words refer to Avenue Therapeutics, Inc. and its consolidated subsidiaries.

Our Business

Overview and Product Candidate Development

We are a specialty pharmaceutical company that seeks to develop and commercialize therapies for the treatment of rare and neurologic diseases. Our current product candidates include AJ201 for the treatment of spinal and bulbar muscular atrophy ("SBMA"), intravenous ("IV") Tramadol ("IV Tramadol") for the treatment of post-operative acute pain, and BAER-101 for the treatment of epilepsy and panic disorders. We may in the future acquire additional product candidates.

In November 2022, we completed the transactions contemplated under a Share Contribution Agreement, dated May 11, 2022, with Fortress Biotech, Inc ("Fortress") to acquire shares in Baergic Bio, Inc. ("Baergic"), which is developing BAER-101, a novel $\alpha 2/3$ -subtype-selective GABA A positive allosteric modulator ("PAM"). As a result, Baergic is a majority-controlled and owned subsidiary company of the Company.

In February 2023, we entered into a license agreement with AnnJi Pharmaceutical Co., Ltd. ("AnnJi") whereby the Company obtained an exclusive license from AnnJi to intellectual property rights pertaining to the molecule known as JM17, which activates Nrf1 and Nrf2, enhances androgen receptor degradation and underlies AJ201, a clinical product candidate currently in a Phase 1b/2a clinical trial in the United States ("U.S.") for the treatment of SBMA, also known as Kennedy's Disease.

AJ201

In February 2023, the Company licensed intellectual property rights pertaining to the molecule known as JM17, which activates Nrf1 and Nrf2, enhances androgen receptor degradation and underlies AJ201 from AnnJi. AJ201 is currently in a Phase 1b/2a clinical trial in the U.S. for the treatment of spinal and bulbar muscular atrophy, also known as Kennedy's Disease. SBMA is a rare, inherited, X-linked genetic neuromuscular disease primarily affecting men. The condition is caused by a polyglutamine expansion in the androgen receptor ("AR") which leads to production of an abnormal AR protein that forms aggregates responsible for muscle atrophy focused in the spinal-bulbar region of the body. The weakening of the bulbar muscles affects chewing, speech and swallowing, with patients prone to choking or inhaling foods or liquids, resulting in airway infection. SBMA also affects muscles in the limbs, leading to difficulty walking and injury caused by falling. Currently, there is no effective treatment for SBMA.

AJ201 was designed to modify SBMA through multiple mechanisms including degradation of the abnormal AR protein and by stimulating Nrf1 and Nrf2, which are involved in protecting cells from oxidative stress which can lead to cell death. AJ201 completed a Phase 1 clinical trial in 2021, which demonstrated the safety of the molecule. It is currently being studied in a Phase 1b/2a multicenter, randomized, double-blind clinical trial in six clinical sites across the U.S., and screening of patients with SBMA has begun. This study aims to evaluate the safety and clinical response of AJ201 in patients suffering from SBMA. AJ201 has been granted Orphan Drug Designation by the U.S. Food and Drug Administration ("FDA") for the indications of SBMA, Huntington's Disease and Spinocerebellar Ataxia.

IV Tramadol

Under the terms of certain agreements described herein, we have an exclusive license to develop and commercialize IV Tramadol in the United States. In 2016, we completed a pharmacokinetic study for IV Tramadol in healthy volunteers as well as an end of phase 2 meeting with the U.S. Food and Drug Administration (“FDA”). In the third quarter of 2017, we initiated a Phase 3 development program of IV Tramadol for the management of post-operative pain. In December 2019, we submitted a New Drug Application (“NDA”) for IV Tramadol and received a Complete Response Letter from the FDA in October 2020. In February 2021, we resubmitted the NDA for IV Tramadol. The FDA assigned a Prescription Drug User Fee Act goal date of April 12, 2021 for the resubmitted NDA for IV Tramadol. On June 14, 2021, we announced that we had received a second Complete Response Letter (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 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 incorporated the FDA’s suggestions from the meeting minutes and submitted a detailed study protocol that could form the basis for the submission of a complete response to the Second CRL.

On March 9, 2023, the Company participated in a Type C meeting with the FDA to discuss a proposed study protocol to assess the risk of respiratory depression related to opioid stacking on IV Tramadol relative to an approved opioid analgesic. We continue to evaluate next steps with regard to IV Tramadol.

BAER-101 (novel $\alpha 2/3$ -subtype-selective GABA A PAM)

Through our majority-owned subsidiary, Baergic, we are developing BAER-101, a high affinity, selective modulator of the gamma-aminobutyric acid (“GABA”) A, which is a receptor system with differential binding and modulatory properties dependent on the particular GABA A subtype. Baergic intends to explore BAER-101 in a number of neurologic disorders where patients are not adequately treated.

Relationship with Fortress

We were incorporated in Delaware on February 9, 2015, as a wholly owned subsidiary of Fortress, to develop and market pharmaceutical products for the acute care setting in the United States. Fortress controls a voting majority of our capital stock pursuant to its ownership of a class of preferred stock, some of the features of which have been contractually suspended. We anticipate remaining a majority owned subsidiary of Fortress after the completion of this offering.

Private Placement of Warrants

On January 27, 2023, the Company entered into a Securities Purchase Agreement (the “PIPE Purchase Agreement”) with the Selling Stockholder, an institutional accredited investor, for a private placement offering (“Private Placement”) of warrants (the “warrants”) to purchase 1,940,299 shares of Common Stock. Pursuant to the PIPE Purchase Agreement, the Company agreed to issue and sell the warrants at an offering price of \$0.125 per warrant to purchase one share of Common Stock. The warrants have an exercise price of \$1.55 per share (subject to adjustment as set forth in the warrants), are exercisable six months after issuance and will expire three years from the date on which the warrants become exercisable. The warrants contain standard anti-dilution adjustments to the exercise price including for share splits, share dividend, rights offerings and pro rata distributions.

The Private Placement closed on January 31, 2023, concurrently with an offering to the same institutional accredited investor that was registered under the Securities Act. The gross proceeds to the Company from the Private Placement, before deducting placement agent fees and other estimated offering expenses payable by the Company, were approximately \$0.24 million. The Company intends to use the net proceeds from the private placement for working capital and other general corporate purposes.

In connection with the PIPE Purchase Agreement, the Company entered into a registration rights agreement (the “Registration Rights Agreement”) with the Selling Stockholder. Pursuant to the Registration Rights Agreement, the Company will be required to file, on or prior to April 10, 2023, a resale registration statement with the SEC to register the resale of the shares issuable upon exercise of the warrants. Accordingly, as required by the Registration Rights Agreement, the registration statement of which this prospectus forms a part relates to the offer and resale of the Common Stock issued to the Selling Stockholder under the PIPE Purchase Agreement.

Summary Risk Factors

Our business is subject to risks of which you should be aware before making an investment decision. The risks described below are a summary of the principal risks associated with an investment in us and are not the only risks we face. You should carefully consider these risk factors, the risk factors described under the heading “Risk Factors”, and the other reports and documents that we have filed with the SEC.

Risks Pertaining to Our Business and Influence

- We currently have no drug products for sale, and three drug product candidates, IV Tramadol, BAER-101 and AJ201. We are dependent on the success of our product candidates, and cannot guarantee that our product candidates will receive regulatory approval or be successfully commercialized.
- If serious adverse or unacceptable side effects are identified during the development of our current or future product candidates, we may need to abandon or limit our development of some of our product candidates.
- There is no assurance that we will be able to successfully integrate Baergic Bio, Inc. or develop BAER-101 or AJ201.
- We are a “smaller reporting company,” and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

Risks Pertaining to Our Finances

- There is substantial doubt about our ability to continue as a going concern, which may hinder our ability to obtain future financing.
- We have incurred significant losses since our inception. We expect to incur losses for the foreseeable future, and may never achieve or maintain profitability.
- We will require substantial additional funding, which may not be available to us on acceptable terms, or at all. If we fail to raise the necessary additional capital, we may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our product development programs or commercialization efforts.
- We do not have any products that are approved for commercial sale and therefore do not expect to generate any revenues from product sales in the foreseeable future, if ever.
- Raising additional capital may cause dilution to our existing stockholders, restrict our operations, or require us to relinquish proprietary rights.

Risks Pertaining to Reliance on Third Parties

- We rely, and expect to continue to rely, on third parties to conduct our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials or complying with applicable regulatory requirements.
- We rely on third parties to manufacture our products and their failure to produce the product in the volumes that we require on a timely basis, to produce the product according to the applicable quality standards and requirements, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the commercialization of this product candidate, lose potential revenues or be unable to meet market demand.
- We rely on clinical data and results obtained by third parties that could ultimately prove to be inaccurate or unreliable.

Risks Pertaining to Regulatory Approval Process

- We may not receive regulatory approval for our product candidates, or our approval may be significantly delayed due to scientific or regulatory reasons.
- Even if one or more of our product candidates receives regulatory approval, which may not occur, it will remain subject to substantial regulatory scrutiny.
- Our current and future relationships with customers and third-party payors in the United States and elsewhere may be subject, directly or indirectly, to applicable anti-kickback, fraud and abuse, false claims, transparency, health information privacy and security and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, administrative burdens and diminished profits and future earnings.
- Regulatory approval for any approved product is limited by the FDA to those specific indications and conditions for which clinical safety and efficacy have been demonstrated.
- If the Drug Enforcement Agency decides to reschedule Tramadol from a Schedule IV controlled substance to a more restrictive Schedule, IV Tramadol could lose its competitive advantage, and our related clinical development and regulatory approval could be delayed or prevented.

Risks Pertaining to the Commercialization of Product Candidates

- We are subject to new legislation, regulatory proposals and managed care initiatives that may increase our costs of compliance and adversely affect our ability to market our products, obtain collaborators and raise capital.
- Public concern regarding the safety of opioid drug products such as IV Tramadol could delay or limit our ability to obtain regulatory approval, result in the inclusion of serious risk information in our labeling, negatively impact market performance, or require us to undertake other activities that may entail additional costs.
- We expect intense competition for our product candidates, and new products may emerge that provide different or better therapeutic alternatives for our targeted indications.
- If the government or third-party payors fail to provide adequate coverage and payment rates for our product candidates or any future products we may license or acquire in the future, if any, or if hospitals choose to use therapies that are less expensive, our potential revenue and prospects for profitability will be limited.
- If we are unable to establish sales, and marketing capabilities or to enter into agreements with third parties to market and sell our product candidate, we may not be successful in commercializing our product candidates if and when they are approved.
- We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability for our product candidates or other product candidates we may license or acquire and may have to limit their commercialization.

Risks Pertaining to Intellectual Property and Potential Disputes Thereof

- If we are unable to obtain and maintain patent protection for our technology and products or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and products similar or identical to ours, and our ability to successfully commercialize our technology and products may be impaired.
- If we are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in any litigation would harm our business.
- If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.
- If we fail to comply with our obligations in our intellectual property licenses and funding arrangements with third parties, we could lose rights that are important to our business.

Risks Pertaining to the Influence of Fortress

- Fortress controls a voting majority of our common stock and has the rights to receive significant share grants annually, which will result in dilution of our other stockholders and could reduce the value of our common stock.
- We have entered into certain agreements with Fortress and may have received better terms from unaffiliated third parties.

Corporate Information

We are a majority-controlled subsidiary of Fortress. Baergic Bio is our sole subsidiary.

Avenue Therapeutics, Inc. was incorporated in Delaware on February 9, 2015. Our executive offices are located at 1111 Kane Concourse, Suite 201, Bay Harbor Islands Florida, 33154. Our telephone number is (781) 652-4500, and our email address is info@avenuetx.com. Information on our website, or any other website, is not incorporated by reference in this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

THE OFFERING

| | |
|--|---|
| Issuer | Avenue Therapeutics, Inc. |
| Securities Offered by Selling Stockholder: | 1,940,299 shares of the Company's Common Stock issuable upon exercise of certain warrants held by the Selling Stockholder (including shares that may be issued to the holder in lieu of fractional shares). |
| Shares of Common Stock Outstanding Prior to this Offering⁽¹⁾: | 5,931,012 |
| Shares of Common Stock Outstanding assuming exercise of all Warrants⁽¹⁾: | 7,871,311 |

Terms of the Offering

The Selling Stockholder will determine when and how it will sell the Common Stock offered in this prospectus, as described in the section of this prospectus titled “*Plan of Distribution*.”

Use of Proceeds:

We will not receive any proceeds from the sale of the Common Stock by the Selling Stockholder in this offering. See “*Use of Proceeds*.”

Risk Factors:

See “*Risk Factors*” incorporated by reference into this prospectus from our most current Annual Report on Form 10-K and subsequent Quarterly Reports on Form 10-Q for a discussion of certain factors you should carefully consider before deciding to invest in shares of our Common Stock.

Nasdaq Capital Market Symbol:

ATXI

(1) The number of shares of Common Stock outstanding before and after this offering is based on 5,931,012 shares of our Common Stock outstanding as of March 28, 2023, and excludes:

- 6,078,132 shares of Common Stock issuable upon exercise of outstanding warrants having a weighted-average exercise price of \$1.55 per share;
- 1,092,299 shares of Common Stock issuable upon exercise of outstanding pre-funded warrants having a nominal exercise price per share;
- 13,137 shares of Common Stock issuable upon the vesting and settlement of outstanding restricted stock award/units;
- 5,122,489 shares of Common Stock reserved for issuance and available for future grant under our 2015 Incentive Plan; and
- 831,618 shares of Common Stock issuable to AnnJi Pharmaceutical Co. Ltd., in connection with the license agreement executed in February 2023

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus 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 prospectus, 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, as they relate to us, are generally 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:

- the fact that we currently have no drug products for sale and that our success is dependent on our product candidates receiving regulatory approval and being successfully commercialized;
- the possibility that serious adverse or unacceptable side effects are identified during the development of our current or future product candidates, such that we would need to abandon or limit development of some of our product candidates;
- our ability to successfully integrate Baergic Bio, Inc. or develop BAER-101 or AJ201;
- the substantial doubt raised about our ability to continue as a going concern, which may hinder our ability to obtain future financing;
- the significant losses we have incurred since inception and our expectation that we will continue to incur losses for the foreseeable future;
- our need for substantial additional funding, which may not be available to us on acceptable terms, or at all, which unavailability could force us to delay, reduce or eliminate our product development programs or commercialization efforts;
- our reliance on third parties for several aspects of our operations;
- our reliance on clinical data and results obtained by third parties that could ultimately prove to be inaccurate or unreliable;
- the possibility that we may not receive regulatory approval for any or all of our product candidates, or that such approval may be significantly delayed due to scientific or regulatory reasons;
- the fact that even if one or more of our product candidates receives regulatory approval, they will remain subject to substantial regulatory scrutiny;
- the effects of current and future laws and regulations relating to fraud and abuse, false claims, transparency, health information privacy and security and other healthcare laws and regulations;
- the effects of competition for our product candidates and the potential for new products to emerge that provide different or better therapeutic alternatives for our targeted indications;
- the possibility that the government or third-party payors fail to provide adequate coverage and payment rates for our product candidates or any future products;

- our ability to establish sales and marketing capabilities or to enter into agreements with third parties to market and sell our product candidates;

- our exposure to potential product liability claims;
- related to the protection of our intellectual property and our potential inability to maintain sufficient patent protection for our technology and products;
- our ability to maintain compliance with the obligations under our intellectual property licenses and funding arrangements with third parties, without which licenses and arrangements we could lose rights that are important to our business;
- the fact that Fortress controls a voting majority of our common stock and has rights to receive significant share grants annually; and
- those risks discussed in “*Risk Factors*” elsewhere in this prospectus, as well as those described in any other 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, except as required by applicable law. Investors should evaluate any statements made by us in light of these important factors.

MARKET AND INDUSTRY DATA AND FORECASTS

We obtained the industry and market data used throughout this prospectus from our own internal estimates and research, as well as from independent market research, industry and general publications and surveys, governmental agencies, publicly available information and research, surveys and studies conducted by third parties. Internal estimates are derived from publicly available information released by industry analysts and third-party sources, our internal research and our industry experience, and are based on assumptions made by us based on such data and our knowledge of our industry and market, which we believe to be reasonable. In some cases, we do not expressly refer to the sources from which this data is derived. In addition, while we believe the industry and market data included in this prospectus is reliable and based on reasonable assumptions, such data involve material risks and other uncertainties and are subject to change based on various factors, including those discussed in the section titled “*Risk Factors*.” These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties or by us.

RISK FACTORS

Investing in our Common Stock involves a high degree of risk. Our business is influenced by many factors that are difficult to predict, involve uncertainties that may materially affect actual results and are often beyond our control. We have identified a number of these factors under the heading “*Risk Factors*” in our Annual Report on Form 10-K for the year ended December 31, 2022, as updated by our subsequently filed Quarterly Reports on Form 10-Q, each of which are incorporated by reference in this prospectus, as well as in other information included or incorporated by reference in this prospectus and any prospectus supplement. You should consider carefully these risks and uncertainties before deciding to invest in our Common Stock. If any of the risks identified as risk factors in the incorporated documents were to materialize, our business, financial condition, results of operations, and future growth prospects could be materially and adversely affected. In that event, the market price of our Common Stock could decline, and you could lose part of or all of your investment in our Common Stock. See the section of this prospectus titled “*Where You Can Find More Information*.”

DIVIDEND POLICY

We currently intend to retain all available funds and any future earnings to fund the growth and development of our business. We have never declared or paid any cash dividends on our Common Stock. We do not intend to pay cash dividends on our Common Stock in the foreseeable future. Investors should not purchase our Common Stock with the expectation of receiving cash dividends.

8

Any future determination to declare dividends will be made at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements, general business conditions, and other factors that our board of directors may deem relevant.

USE OF PROCEEDS

We will not receive any proceeds from the sale of the Common Stock covered by this prospectus and any accompanying prospectus supplement. All proceeds from the sale of the Common Stock will be for the respective accounts of the Selling Stockholder named herein.

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

DETERMINATION OF OFFERING PRICE

We cannot currently determine the price or prices at which the shares of common stock may be sold by the Selling Stockholder under this prospectus.

9

THE SELLING STOCKHOLDER

The shares of Common Stock being offered by the Selling Stockholder are those previously issued to the Selling Stockholder, and those issuable to the Selling Stockholder, in each case, upon exercise of the warrants. For additional information regarding the issuances of those shares of Common Stock and warrants, see “*Prospectus Summary – Private Placement of Warrants*” above. We are registering the resale of the shares of Common Stock in order to permit the Selling Stockholder to offer the shares for resale from time to time. Except for the ownership of the shares of Common Stock and the warrants as well as its purchase of other securities from us in the past, the Selling Stockholder has not had any material relationship with us within the past three years.

The table below lists the Selling Stockholder and other information regarding the beneficial ownership of the shares of Common Stock by the Selling Stockholder. The second column lists the number of shares of Common Stock beneficially owned by the Selling Stockholder, based on its ownership of the shares of Common Stock and warrants, as well as any other securities of ours owned by the Selling Stockholder, as of April 6, 2023, assuming exercise of the warrants held by the Selling Stockholder on that date, without regard to any limitations on exercises.

The third column lists the shares of Common Stock being offered by this prospectus by the Selling Stockholder.

In accordance with the terms of the Registration Rights Agreement with the Selling Stockholder, this prospectus generally covers the resale of the sum of (i) the number of shares of Common Stock issued to the Selling Stockholder in the transaction described under “Prospectus Summary - Private Placement of Warrants” described above and (ii) the maximum number of shares of Common Stock issuable upon exercise of the related warrants, determined as if the outstanding warrants were exercised in full as of the trading day immediately preceding the date this registration statement was initially filed with the SEC, each as of the trading day immediately preceding the applicable date of determination and all subject to adjustment as provided in the Registration Rights Agreement, without regard to any limitations on the exercise of the warrants. The third and fourth column assumes the sale of all of the shares offered by the Selling Stockholder pursuant to this prospectus.

Under the terms of the warrants, a selling stockholder may not exercise the warrants to the extent such exercise would cause such selling stockholder, together with its affiliates and attribution parties, to beneficially own a number of shares of Common Stock which would exceed 4.99% or 9.99%, as applicable, of our then-outstanding Common Stock following such exercise, excluding for purposes of such determination shares of Common Stock issuable upon exercise of the warrants that have not been exercised. The number of shares in the second column does not reflect this limitation. The Selling Stockholder may sell all, some or none of its shares in this offering. See “Plan of Distribution.”

| Selling Stockholder ⁽¹⁾ | Shares Beneficially Owned Immediately Prior to the Offering | Shares Being Offered for Resale Under this Prospectus | Number of Shares Beneficially Owned After Sale of Shares ⁽²⁾ | Percentage of Outstanding Shares of Common Stock Beneficially Owned Immediately Following the Sale of Shares ⁽³⁾ |
|--|--|--|--|---|
| Sabby Volatility Warrant Master Fund, Ltd. | 3,887,489 ⁽⁴⁾ | 1,940, 299 | 1,947,190 ⁽⁵⁾ | 9.99 ⁽⁵⁾ % |

- (1) The principal business address and address for notice to the Selling Stockholder will be the address set forth in our books and records.
- (2) Assumes the Selling Stockholder sells all of the shares of Common Stock being offered by this prospectus.
- (3) Percentage calculated based upon the assumption that the Selling Stockholders sell all of the shares of Common Stock offered by this prospectus.
- (4) Consists of (i) Warrants to purchase up to 1,940,299 shares of Common Stock with an exercise price of \$1.55 per share with the beneficial ownership not to exceed 4.99% and warrants to purchase up to 787,800 shares of Common Stock with an exercise price of \$1.55 per share with the beneficial ownership not to exceed 4.99%, (ii) Pre-Funded Warrants to purchase up to 792,299 shares of Common Stock with the beneficial ownership not to exceed 9.99%, and (iii) 367,091 shares of Common Stock. Sabby Management, LLC, the investment manager of Sabby Volatility Warrant Master Fund, Ltd., and Hal Mintz, manager of Sabby Management, LLC, may be deemed to share voting and dispositive power with respect to these securities. Each of Sabby Management, LLC and Hal Mintz disclaims beneficial ownership over the securities listed except to the extent of their pecuniary interest therein.
- (5) At no point will ownership of shares exceed 4.99% or 9.99% as applicable.

10

PLAN OF DISTRIBUTION

The Selling Stockholder of the securities and any of its pledgees, assignees and successors-in-interest may, from time to time, sell any or all of its securities covered hereby on The Nasdaq Capital Market or any other stock exchange, market or trading facility on which the securities are traded or in private transactions. These sales may be at fixed or negotiated prices. The Selling Stockholder may use any one or more of the following methods when selling securities:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the securities as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- settlement of short sales;
- in transactions through broker-dealers that agree with the Selling Stockholder to sell a specified number of such securities at a stipulated price per security;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- a combination of any such methods of sale; or
- any other method permitted pursuant to applicable law.

The Selling Stockholder may also sell securities under Rule 144 or any other exemption from registration under the Securities Act, if available, rather than under this prospectus.

Broker-dealers engaged by the Selling Stockholder may arrange for other brokers-dealers to participate in sales. Broker-dealers may receive commissions or discounts from the Selling Stockholder (or, if any broker-dealer acts as agent for the purchaser of securities, from the purchaser) in amounts to be negotiated, but, except as set forth in a supplement to this prospectus, in the case of an agency transaction not in excess of a customary brokerage commission in compliance with FINRA Rule 2121; and in the case of a principal transaction a markup or markdown in compliance with FINRA Rule 2121.

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

11

The Selling Stockholder and any broker-dealers or agents that are involved in selling the securities may be deemed to be “underwriters” within the meaning of the Securities Act in connection with such sales. In such event, any commissions received by such broker-dealers or agents and any profit on the resale of the securities purchased by them may be deemed to be underwriting commissions or discounts under the Securities Act. Each Selling Stockholder has informed the Company that it does not have any written or oral agreement or understanding, directly or indirectly, with any person to distribute the securities.

The Company is required to pay certain fees and expenses incurred by the Company incident to the registration of the securities. The Company has agreed to indemnify the Selling Stockholder against certain losses, claims, damages and liabilities, including liabilities under the Securities Act.

We have agreed to keep this prospectus effective until the earlier of (i) the date on which the securities may be resold by the Selling Stockholder without registration and without regard to any volume or manner-of-sale limitations by reason of Rule 144, without the requirement for the Company to be in compliance with the current public information under Rule 144 under the Securities Act or any other rule of similar effect or (ii) all of the securities have been sold pursuant to this prospectus or Rule 144 under the Securities Act or any other rule of similar effect. The resale securities will be sold only through registered or licensed brokers or dealers if required under applicable state securities laws. In addition, in certain states, the resale securities covered hereby may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and is complied with.

Under applicable rules and regulations under the Securities Exchange Act of 1934, as amended (the “Exchange Act”), any person engaged in the distribution of the resale securities may not simultaneously engage in market making activities with respect to the Common Stock for the applicable restricted period, as defined in Regulation M, prior to the commencement of the distribution. In addition, the Selling Stockholder will be subject to applicable provisions of the Exchange Act and the rules and regulations thereunder, including Regulation M, which may limit the timing of purchases and sales of the Common Stock by the Selling Stockholder or any other person. We will make copies of this prospectus available to the Selling Stockholder and have informed it of the need to deliver a copy of this prospectus to each purchaser at or prior to the time of the sale (including by compliance with Rule 172 under the Securities Act).

DESCRIPTION OF SECURITIES TO BE REGISTERED

Avenue Therapeutics has one class of securities registered under Section 12 of the Securities Act of 1934, as amended: our Common Stock. The following description of our Common Stock is a summary and is qualified in its entirety by reference to our Third Amended and Restated Certificate of Incorporation, as amended (“Certificate of Incorporation”), and our Second Amended and Restated Bylaws (the “Bylaws”), which are included as exhibits to the registration statement on Form S-1 of which this prospectus forms a part. We encourage you to read the Certificate of Incorporation and Bylaws as well as the applicable provisions of the General Corporation Law of the State of Delaware, as amended (the “DGCL”), for more information.

Authorized Capital Stock

Our authorized capital stock consists of 75,000,000 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 March 28, 2023, there were 5,931,012 shares of our Common Stock outstanding held by 35 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. However, the holders of our outstanding Class A Preferred Stock, which is held exclusively by Fortress, are entitled to cast, for each share of Class A Preferred Stock, the number of votes that is equal to 1.1 times a fraction, the numerator of which is the sum of (A) the aggregate number of shares of outstanding Common Stock and (B) the whole shares of Common Stock into which the shares of outstanding the Class A Preferred Stock are convertible and the denominator of which is the aggregate number of shares of outstanding Class A Preferred Stock. Thus, Fortress, so long as it holds all shares of our Class A Preferred Stock, will at all times have voting control of us. Further, for a period of ten years from the date of the first issuance of shares of Class A Preferred Stock, 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, are entitled to appoint or elect the majority of our directors, however, the Company and Fortress have historically elected to waive application of this provision of the certificate of incorporation, and instead the holders of the Common Stock have voted together with the holders of the Class A Preferred Stock for all directors at our annual meetings of stockholders, with the holders of the Class A Preferred Stock utilizing the supervoting rights described above.

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.

Provisions of the DGCL and our Certificate of Incorporation and Bylaws could make it more difficult to acquire Avenue Therapeutics 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 Bylaws 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 Bylaws 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.

Warrants Held by the Selling Stockholder

Exercisability

The warrants issued on January 31, 2023 (the “**2023 Warrants**”) to the Selling Stockholder became exercisable upon issuance and at any time up to the date that is three (3) years after their original issuance. The 2023 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 2023 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 2023 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 2023 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 2023 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 2023 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 2023 Warrants may be offered for sale, sold, transferred or assigned without our consent.

Exchange Listing.

The 2023 Warrants are not listed on any securities exchange or nationally recognized trading system.

Fundamental Transactions

In the event of a fundamental transaction, as described in the 2023 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 2023 Warrants will be entitled to receive upon exercise of the 2023 Warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the 2023 Warrants immediately prior to such fundamental transaction.

Rights as a Stockholder

Except as otherwise provided in the 2023 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 2023 Warrants are governed by New York law.

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 Therapeutics only if he or she is a director of Avenue Therapeutics and is acting in his or her capacity as director, and do not apply to officers of Avenue Therapeutics 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 Bylaws 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 Therapeutics or, while a director, officer or employee of Avenue Therapeutics, is or was serving at our request 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 Bylaws 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 Bylaws.

The limitation of liability and indemnification provisions in our Certificate of Incorporation and Bylaws 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 Bylaws 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 Bylaws or otherwise. Any amendment, alteration or repeal of our Bylaws' indemnification provisions is, by the terms of our Bylaws, 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.

MATERIAL UNITED STATES FEDERAL INCOME TAX CONSIDERATIONS

The following discussion summarizes certain U.S. federal income tax considerations of the acquisition, ownership and disposition of the Common Stock offered by this prospectus but does not purport to be a complete analysis of all potential tax effects. This discussion does not address effects of other U.S. federal tax laws, such as estate and gift tax laws, or of state, local, non-U.S. or other tax considerations that may be relevant to a purchaser or holder of the Common Stock in light of their particular circumstances. This discussion is based on the U.S. Internal Revenue Code of 1986, as amended (the "Code"), the Treasury regulations promulgated thereunder, judicial decisions, and published rulings and administrative pronouncements of the U.S. Internal Revenue Service (the "IRS"), in each case as of the date hereof. These authorities may change, possibly with retroactive effect, or may be subject to differing interpretations that may adversely affect a holder of the Common Stock. There can be no assurance the IRS or a court will not take a contrary position to that discussed below regarding the acquisition, ownership and disposition of the Common Stock.

This discussion is limited to holders that hold the Common Stock as a capital asset within the meaning of Section 1221 of the Code (generally property held for investment). This discussion does not describe all of the U.S. federal income tax consequences that may be relevant to a holder in light of its particular circumstances, including the impact of the alternative minimum tax and of the Medicare contribution tax on net investment income. In addition, it does not address consequences for holders subject to special rules, including without limitation:

- U.S. expatriates and former citizens or long-term residents of the United States;
- persons holding the Common Stock as part of a hedge, straddle, conversion, or other integrated transaction;
- banks, insurance companies, and other financial institutions;
- brokers, dealers or traders in securities;
- "controlled foreign corporations," "passive foreign investment companies," and corporations that accumulate earnings to avoid U.S. federal income tax;
- S corporations or entities or arrangements that are treated as partnerships for U.S. federal income tax purposes (and investors therein);
- tax-exempt organizations or governmental organizations;
- real estate investment trusts or regulated investment companies;
- U.S. persons whose functional currency is not the U.S. dollar;
- persons subject to special tax accounting rules;
- persons who hold or receive the Common Stock pursuant to the exercise of any employee stock option or otherwise as compensation;
- persons deemed to sell our Common Stock under the constructive sale provisions of the Code;

- tax-qualified retirement plans, individual retirement accounts or other tax-deferred accounts; and
- “qualified foreign pension funds” as defined in Section 897(l)(2) of the Code.

If a partnership (or any other entity treated as a partnership for U.S. federal income tax purposes) holds the Common Stock, the U.S. federal income tax treatment of a partner of that partnership generally will depend upon the status of the partner and the activities of the partnership. If you are a partnership or a partner of a partnership holding the Common Stock, you should consult your tax advisors as to the particular U.S. federal income tax consequences of holding and disposing of the Common Stock.

This discussion is for informational purposes only and is not tax advice. You should consult your own independent tax advisor concerning the application of the U.S. federal income tax laws to your particular circumstances as well as any tax consequences for the acquisition, ownership, or disposition of the Common Stock arising under other U.S. federal tax laws and the laws of any state, local or non-U.S. tax jurisdiction or under any applicable income tax treaty.

For purposes of this discussion, a “U.S. holder” is a beneficial owner of our Common Stock that, for U.S. federal income tax purposes, is or is treated as:

- an individual who is a citizen or resident of the United States;
- a corporation created or organized under the laws of the United States, any state thereof, or the District of Columbia;
- an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- a trust that (i) is subject to the primary supervision of a U.S. court and the control of one or more “United States persons” (within the meaning of Section 7701(a)(30) of the Code) or (ii) has a valid election in effect to be treated as a United States person for U.S. federal income tax purposes.

A “non-U.S. holder” is any beneficial owner of our Common Stock that is not a U.S. holder.

U.S. Holders

Distributions in General

If distributions are made with respect to the Common Stock, such distributions will be treated as dividends to the extent of our current or accumulated earnings and profits as determined under the Code. Subject to customary conditions and limitations, dividends will be eligible for the dividends-received deduction in the case of U.S. holders that are (or are treated for U.S. federal income tax purposes) as corporations. Dividends paid to non-corporate U.S. holders generally will qualify for taxation at preferential rates if those holders meet certain holding period and other applicable requirements. Dividends received by non-corporate U.S. holders may also be subject to the additional 3.8% tax on net investment income. Any portion of a distribution that exceeds our current and accumulated earnings and profits will first be applied to reduce a U.S. holder’s tax basis in the Common Stock, but not below zero. Distributions in excess of our current and accumulated earnings and profits and in excess of a U.S. holder’s tax basis in its shares will be taxable as gain from the disposition of the Common Stock, the tax treatment of which is discussed below.

Extraordinary Dividends

Dividends that exceed certain thresholds in relation to a U.S. holder’s tax basis in the Common Stock could be characterized as “extraordinary dividends” under Section 1059 of the Code. Corporate U.S. holders that have held our Common Stock for two years or less before the dividend announcement date and that receive an extraordinary dividend will generally be required to reduce their tax basis in the stock by the nontaxed portion of the dividend due to the dividends-received deduction. If the amount of reduction exceeds the U.S. holder’s tax basis in the stock, the excess will be taxable as gain from the disposition of the stock, the tax treatment of which is discussed below. Non-corporate U.S. holders that receive an extraordinary dividend will be required to treat any losses on the sale of our Common Stock as long-term capital losses to the extent of the extraordinary dividends such U.S. holders receive that qualify for taxation at the preferential rates discussed above under “—*Distributions in General.*” U.S. holders are urged to consult their tax advisors with respect to the eligibility for and amount of any dividend received deduction and the application of Section 1059 of the Code to any dividends they receive.

Disposition of Common Stock by Sale, Exchange or Redemption

Upon any sale or disposition (other than certain redemptions, as discussed below) of the Common Stock, a U.S. holder generally will recognize capital gain or loss equal to the difference between the amount realized by the U.S. holder and the U.S. holder’s adjusted tax basis in the Common Stock. Such capital gain or loss will be long-term capital gain or loss if the U.S. holder’s holding period for the Common Stock is longer than one year. Non-corporate U.S. holders may be eligible for preferential tax rates on long-term capital gains but also may be subject to the additional 3.8% tax on net investment income. The deductibility of capital losses is subject to limitations.

A redemption of the Common Stock will be treated as a sale or exchange described in the preceding paragraph if the redemption, based on the facts and circumstances, is treated for U.S. federal income tax purposes as (i) a “complete termination” of your interest in the Common Stock, (ii) a “substantially disproportionate” redemption of your Common Stock, or (iii) is “not essentially equivalent to a dividend”, each within the meaning of Section 302 of the Code. In determining whether any of these tests has been met, you must take into account not only the Common Stock and other equity interests that you actually own but also other equity interests that you constructively own under U.S. federal income tax rules.

If you meet none of the alternative tests described above, the redemption will be treated as a distribution subject to the rules described under “—*Distributions In General.*” If a redemption of the Common Stock is treated as a distribution that is taxable as a dividend, you are urged to consult your tax advisor regarding the allocation of your tax basis as between the redeemed and remaining shares of Common Stock.

Information Reporting and Backup Withholding

We or an applicable withholding agent will report to our U.S. holders and the IRS the amount of dividends (including deemed dividends) paid during each year and the amount of any tax withheld with respect to the Common Stock. Certain non-corporate U.S. holders may be subject to U.S. backup withholding at a rate of 28% on payments of dividends on the Common Stock unless the holder furnishes the payor or its agent with a taxpayer identification number, certified under penalties of perjury, and certain other information or otherwise establishes an exemption from backup withholding. Backup withholding tax is not an additional tax. Any amounts withheld under the backup withholding rules may be allowed as a refund or a credit against a U.S. holder’s U.S. federal income tax liability, provided the U.S. holder timely furnishes the required

information to the IRS.

Non-U.S. Holders

Distributions

If distributions are made with respect to the Common Stock, such distributions will be treated as dividends to the extent of our current or accumulated earnings and profits as determined under the Code and may be subject to withholding as discussed below. Any portion of a distribution that exceeds our current and accumulated earnings and profits will first be applied to reduce the Non-U.S. holder's basis in the Common Stock, but not below zero. If the distribution exceeds our current and accumulated earnings and profits and the Non-U.S. holder's basis, the excess will be treated as gain from the disposition of the Common Stock, the tax treatment of which is discussed below.

In addition, if we are classified as a U.S. real property holding corporation (a "USRPHC") within the meaning of Section 897(c) of the Code and any distribution exceeds our current and accumulated earnings and profits, we will need to satisfy our withholding requirements either by (a) treating the entire distribution (even if in excess of earnings and profits) as a dividend subject to the withholding rules described below and withhold at a minimum rate of 15% or such lower rate as may be specified by an applicable income tax treaty for distributions from a USRPHC; or (b) treating (i) only the amount of the distribution equal to our reasonable estimate of our current and accumulated earnings and profits as a dividend subject to the withholding rules in the following paragraph; and (ii) the excess portion of the distribution as subject to withholding at a rate of 15% (or such lower rate as may be specified by an applicable income tax treaty), as if such excess were the result of a sale of shares in a USRPHC, with a credit generally allowed against the Non-U.S. holder's U.S. federal income tax liability for the tax withheld from such excess. We believe that we currently are not a USRPHC, and we do not expect to become a USRPHC for the foreseeable future (see discussion of USRPHCs below under "*Disposition of Common Stock, Including Redemptions*").

Dividends (including amounts distributed by a USRPHC and subject to withholding as dividends per the preceding paragraph) paid to a Non-U.S. holder of the Common Stock will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty. However, dividends that are treated as being effectively connected with the conduct of a trade or business by the Non-U.S. holder within the United States (and, where a tax treaty applies, are attributable to a permanent establishment maintained by the Non-U.S. holder in the United States) are not subject to this withholding tax, provided that certain certification and disclosure requirements are satisfied including completing IRS Form W-8ECI (or other applicable form). Instead, such dividends are subject to U.S. federal income tax on a net income basis in the same manner as if the Non-U.S. holder were a United States person (as defined under the Code), unless an applicable income tax treaty provides otherwise. Any such effectively connected dividends received by a foreign corporation may be subject to an additional "branch profits tax" at a 30% rate or such lower rate as may be specified by an applicable income tax treaty.

A Non-U.S. holder of the Common Stock who wishes to claim the benefit of an applicable treaty rate and avoid backup withholding for dividends, as discussed below, will be required to (i) complete IRS Form W-8BEN or Form W-8BEN-E (or other applicable form) and certify under penalty of perjury that such holder is not a United States person as defined under the Code and is eligible for treaty benefits, or (ii) if the Common Stock is held through certain foreign intermediaries, satisfy the relevant certification requirements of applicable Treasury regulations. A Non-U.S. holder of the Common Stock eligible for a reduced rate of U.S. withholding tax pursuant to an income tax treaty may obtain a refund of any excess amounts withheld by timely filing an appropriate claim for refund with the U.S. Internal Revenue Service.

Disposition of Common Stock, Including Redemptions

Any gain realized by a Non-U.S. holder on the disposition of the Common Stock generally will not be subject to U.S. federal income or withholding tax unless:

- the gain is effectively connected with the conduct of a trade or business by the Non-U.S. holder in the United States (and, if required by an applicable income tax treaty, attributable to a permanent establishment maintained by the Non-U.S. holder in the United States);
- the Non-U.S. holder is an individual who is present in the United States for 183 days or more in the taxable year of disposition, and certain other conditions are met; or
- we are or have been a USRPHC, as defined in Section 897(c) of the Code, and a Non-U.S. holder owned directly or pursuant to applicable attribution rules at any time during the five-year period ending on the date of disposition more than 5% of the Common Stock — assuming that the Common Stock is regularly traded on an established securities market, within the meaning of Section 897(c)(3) of the Code.

A Non-U.S. holder described in the first bullet point immediately above will generally be subject to tax on the gain derived from the sale under regular graduated U.S. federal income tax rates in the same manner as if the Non-U.S. holder were a United States person as defined under the Code, and, if it is a corporation, may also be subject to branch profits tax equal of 30% (generally applicable to its effectively connected earnings and profits) or at such lower rate as may be specified by an applicable income tax treaty.

An individual Non-U.S. holder described in the second bullet point immediately above will be subject to a flat 30% tax (or at such reduced rate as may be provided by an applicable tax treaty) on the gain derived from the sale, which may be offset by U.S. source capital losses, even if the individual is not considered a resident of the United States for U.S. federal income tax purposes.

A Non-U.S. holder described in the third bullet point above will be subject to U.S. federal income tax under regular graduated U.S. federal income tax rates with respect to the gain realized in the same manner as if the Non-U.S. holder were a United States person as defined under the Code. A corporation is a USRPHC if it is a U.S. corporation and the fair market value of its U.S. real property interests equals or exceeds 50% of the sum of the fair market value of its worldwide real property interests and its other assets used or held for use in a trade or business. We believe that we currently are not a USRPHC for U.S. federal income tax purposes, and we do not expect to become a USRPHC for the foreseeable future. Our Common Stock is listed on the NASDAQ Capital Market and we believe that, for as long as we continue to be so listed, our Common Stock will be treated as regularly traded on an established securities market. However, if we become a USRPHC and our Common Stock is regularly traded on an established securities market, a Non-U.S. holder generally will be subject to U.S. federal income tax on any gain from the disposition of such stock if such Non-U.S. holder has owned or is deemed to have owned more than 5% of our Common Stock, at any time within the shorter of the five-year period preceding the disposition or such holder's holding period for such stock.

If a Non-U.S. holder is subject to U.S. federal income tax on any sale, exchange, redemption (except as discussed below), or other disposition of the Common Stock, the Non-U.S. holder will recognize capital gain or loss equal to the difference between the amount realized by the Non-U.S. holder and the Non-U.S. holder's adjusted tax basis in the Common Stock. Such capital gain or loss will be long-term capital gain or loss if the Non-U.S. holder's holding period for the Common Stock is longer than one year. A Non-U.S. holder should consult its own independent tax advisors with respect to applicable tax rates and netting rules for capital gains and losses. Certain limitations exist on the deduction of capital losses by both corporate and non-corporate taxpayers.

If a Non-U.S. holder is subject to U.S. federal income tax on any disposition of the Common Stock, a redemption of shares of the Common Stock will be a taxable event. If the

redemption is treated as a sale or exchange, instead of as a dividend, a Non-U.S. holder generally will recognize capital gain or loss, equal to the difference between the amount of cash received and fair market value of any property received and the Non-U.S. holder's adjusted tax basis in the Common Stock redeemed (except that to the extent that any cash received is attributable to any accrued but unpaid dividends), and such capital gain or loss will be long-term capital gain or loss if the Non-U.S. holder's holding period for such Common Stock exceeds one year. A payment made in redemption of the Common Stock may be treated as a dividend (subject to taxation as discussed above under "*Disposition of Common Stock, Including Redemptions*"), rather than as payment in exchange for the Common Stock, in the same circumstances discussed above under "*Disposition of Common Stock, Including Redemptions*." Each Non-U.S. holder of the Common Stock should consult its own independent tax advisors to determine whether a payment made in redemption of the Common Stock will be treated as a dividend or as payment in exchange for the Common Stock.

Information reporting and backup withholding.

We must annually report to the IRS and to each Non-U.S. holder the amount of dividends (including constructive dividends) paid to such Non-U.S. holder and the tax withheld with respect to such dividends, regardless of whether withholding was required. Copies of the information returns reporting such dividends and withholding may also be made available under the provisions of an applicable tax treaty or agreement with the tax authorities in the country in which the non-U.S. holder resides. U.S. backup withholding will generally apply to the payment of dividends to non-U.S. holders unless such non-U.S. holders furnish to the payor an IRS Form W-8BEN or Form W-8BEN-E (or other applicable form) or otherwise establish an exemption.

Payment by a U.S. office of a broker of the proceeds of a sale of shares of our Common Stock is subject to both backup withholding and information reporting unless the non-U.S. holder, or beneficial owner thereof, as applicable, certifies that it is a non-U.S. holder on Form W-8BEN or Form W-8BEN-E (or other suitable substitute or successor form), or otherwise establishes an exemption. Subject to certain exceptions, backup withholding and information reporting generally will not apply to a payment of proceeds from the sale of shares of our Common Stock if such sale is effected through a foreign office of a broker, provided that the broker does not have certain U.S. connections. Any amount withheld under the backup withholding rules from a payment to a non-U.S. holder is allowable as a credit against such holder's U.S. federal income tax liability (if any), which may entitle the holder to a refund if in excess of such liability, provided that the holder timely provides the required information to the IRS. Non-U.S. holders are urged to consult their own tax advisers regarding the application of backup withholding in their particular circumstances and the availability of and procedure for obtaining an exemption from backup withholding under current Treasury Regulations.

Foreign Account Tax Compliance Act.

Sections 1471 to 1474 of the Code (such sections, and the Treasury Regulations and administrative guidance issued thereunder, commonly referred to as FATCA) impose a 30% U.S. withholding tax on certain "withholdable payments" made to a "foreign financial institution" or a "nonfinancial foreign entity." "Withholdable payments" include payments of dividends and the gross proceeds from a disposition of certain property (such as shares of our Common Stock), if such disposition occurs after December 31, 2018. In general, if a holder is a "foreign financial institution" (which includes investment entities such as hedge funds and private equity funds), the 30% withholding tax will apply to withholdable payments made to such holder, unless such holder enters into an agreement with the U.S. Department of Treasury to collect and provide substantial information regarding its U.S. account holders, including certain account holders that are foreign entities with U.S. owners, and to withhold 30% on certain "pass-through payments." If such holder is a "non-financial foreign entity," FATCA also generally will impose a withholding tax of 30% on withholdable payments made to such holder unless the holder provides the withholding agent with a certification that it does not have any "substantial United States owners" or a certification identifying its direct and indirect substantial United States owners. Intergovernmental agreements between the United States and a holder's resident country may modify some of the foregoing requirements.

Although withholding under FATCA would also have applied to payments of gross proceeds from the sale or other disposition of the Common Stock on or after January 1, 2019, Treasury Regulations proposed in late 2018 eliminate FATCA withholding on payments of gross proceeds entirely. Taxpayers generally may rely on these proposed Treasury Regulations until final Treasury Regulations are issued.

We will not pay any additional amounts to holders of the Common Stock in respect of any amounts withheld. Non-U.S. holders should consult their own tax advisers with respect to the U.S. federal income tax consequences of FATCA on their ownership and disposition of shares of our Common Stock.

Documentation that holders provide in order to be treated as FATCA compliant may be reported to the IRS and other tax authorities, including information about a holder's identity, its FATCA status and if applicable, its direct and indirect U.S. owners. Prospective investors should consult their tax advisers about how information reporting and the possible imposition of withholding tax under FATCA may apply to their investment in the Common Stock.

LEGAL MATTERS

McGuireWoods LLP, Charlotte, North Carolina, will pass upon the validity of the securities being offered by this prospectus. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

EXPERTS

The consolidated financial statements of Avenue Therapeutics, Inc. as of December 31, 2022 and for the year ended December 31, 2022 have been incorporated by reference herein and in the registration statement in reliance on the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in auditing and accounting. The audit report covering the December 31, 2022 consolidated financial statements contains an explanatory paragraph that states the Company has incurred substantial operating losses since its inception and expects to continue to incur significant operating losses for the foreseeable future that raise substantial doubt about the Company's ability to continue as a going concern. The consolidated financial statements do not include any adjustments that might result from the outcome of that uncertainty.

The financial statements of Avenue Therapeutics, Inc. as of December 31, 2021 and for the year ended December 31, 2021 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.

The financial statements of Baergic Bio, Inc. as of December 31, 2021 and 2020 and for each of the years in the two-year period ended December 31, 2021, have been incorporated by reference herein and in the registration statement in reliance on the report of KPMG LLP, independent registered public accounting firm, incorporated by reference herein, and upon the authority of said firm as experts in auditing and accounting. The audit report covering the December 31, 2021 financial statements contains an explanatory paragraph that states that the Company's recurring losses from operations raise substantial doubt about the entity's ability to continue as a going concern. The financial statements do not include any adjustments that might result from the outcome of that uncertainty.

WHERE YOU CAN FIND MORE INFORMATION

We file reports and proxy statements with the SEC. These filings include our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and proxy statements on Schedule 14A, as well as any amendments to those reports and proxy statements, which are available free of charge through our website as soon as reasonably practicable after we file them with, or furnish them to, the SEC. Our Internet website address is www.avenuetx.com. Our website and the information contained on, or that can be accessed through, the website will not be deemed to be incorporated by reference in, and are not considered part of, this prospectus. You should not rely on any such information in making your decision whether to purchase our securities. The SEC also maintains a website at www.sec.gov that contains reports, proxy and information statements and other information regarding us and other issuers that file electronically with the SEC.

We have filed with the SEC a registration statement on Form S-1 under the Securities Act relating to the securities being offered by this prospectus. This prospectus, which constitutes part of that registration statement, does not contain all of the information set forth in the registration statement or the exhibits and schedules which are part of the registration statement. For further information about us and the securities offered, see the registration statement and the exhibits and schedules thereto. Statements contained in this prospectus regarding the contents of any contract or any other document to which reference is made are not necessarily complete, and, in each instance where a copy of a contract or other document has been filed as an exhibit to the registration statement, reference is made to the copy so filed, each of those statements being qualified in all respects by the reference.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to “incorporate by reference” into this prospectus the information we file with the SEC in other documents, 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. The information incorporated by reference is considered to be part of this prospectus, and later information that we file with the SEC will automatically update and supersede such information. We incorporate by reference the documents listed below and any future information filed (rather than furnished) with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act between the date of this prospectus and the date all securities to which this prospectus relates have been sold or the offering is otherwise terminated and also between the date of the initial registration statement and prior to effectiveness of the registration statement, provided, however, that we are not incorporating any information furnished under Item 2.02 or Item 7.01 of any Current Report on Form 8-K:

- our Annual Report on Form 10-K for the year ended December 31, 2022, filed with the SEC on [March 31, 2023](#); and
- our Current Reports on Form 8-K and Form 8-K/A filed with the SEC on [March 8, 2023](#), [March 2, 2023](#), [February 10, 2023](#), [February 3, 2023](#), [February 1, 2023](#), [January 25, 2023](#) and [November 8, 2022](#).

We will furnish without charge to you a copy of any or all of the documents incorporated by reference, including exhibits to these documents, upon written or oral request. Direct your request to: Corporate Secretary, Avenue Therapeutics, Inc., 1111 Kane Concourse, Suite 201, Bay Harbor Islands Florida 33154, or (781) 652-4500.

A statement contained in a document incorporated by reference into this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, any prospectus supplement or in any other subsequently filed document which is also incorporated in this prospectus modifies or replaces such statement. Any statements so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.



1,940,299 Shares of Common Stock

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 13. Other Expenses of Issuance and Distribution

The following table indicates the expenses to be incurred in connection with the offering described in this registration statement, other than underwriting discounts and commissions, all of which will be paid by us. All amounts are estimated except the SEC registration fee.

| | Amount |
|------------------------------|---------------|
| SEC registration fee | \$ 255 |
| Accounting fees and expenses | \$ 70,000 |
| Legal fees and expenses | \$ 35,000 |
| Total expenses | \$ 105,255 |

Item 14. Indemnification of Directors and Officers

Under the General Corporation Law of the State of Delaware (“DGCL”), a corporation may include provisions in its certificate of incorporation that will relieve its directors of monetary liability for breaches of their fiduciary duty to the corporation, except under certain circumstances, including a breach of the director’s duty of loyalty, acts or omissions of the director not in good faith or which involve intentional misconduct or a knowing violation of law, the approval of an improper payment of a dividend or an improper purchase by the corporation of stock or any transaction from which the director derived an improper personal benefit. The Company’s Third Amended and Restated Certificate of Incorporation, as amended, eliminates the personal liability of directors to the Company or its stockholders for monetary damages for breach of fiduciary duty as a director with certain limited exceptions set forth in the DGCL.

Section 145 of the DGCL grants to corporations the power to indemnify each officer and director against liabilities and expenses incurred by reason of the fact that he or she is or was an officer or director of the corporation if he or she acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the best interests of the corporation and, with respect to any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful. The Company’s Third Amended and Restated Certificate of Incorporation, as amended, and Second Amended and Restated Bylaws, as amended, provide for indemnification of each officer and director of the Company to the fullest extent permitted by the DGCL. Section 145 of the DGCL also empowers corporations to purchase and maintain insurance on behalf of any person who is or was an officer or director of the corporation against liability asserted against or incurred by him in any such capacity, whether or not the corporation would have the power to indemnify such officer or director against such liability under the provisions of Section 145 of the DGCL.

Item 15. Recent Sales of Unregistered Securities.

Set forth below is information regarding all securities sold by us since April 10, 2020 the offer and sale of which were not registered under the Securities Act. Also included is the consideration received by us for such securities and information relating to the section of the Securities Act, or rule of the SEC, under which exemption from registration was claimed.

On January 27, 2023, the Company entered into a Securities Purchase Agreement (the “PIPE Purchase Agreement”) with an institutional accredited investor, for a private placement offering of warrants to purchase 1,940,299 shares of Common Stock. Pursuant to the PIPE Purchase Agreement, the Company agreed to issue and sell the warrants at an offering price of \$0.125 per warrant to purchase one share of Common Stock. The warrants have an exercise price of \$1.55 per share (subject to adjustment as set forth in the warrants), are exercisable six months after issuance and will expire three years from the date on which the warrants become exercisable. The warrants contain standard anti-dilution adjustments to the exercise price including for share splits, share dividend, rights offerings and pro rata distributions. This private placement closed on January 31, 2023, concurrently with an offering to the same institutional accredited investor that was registered under the Securities Act. The gross proceeds to the Company from the private placement, before deducting placement agent fees and other estimated offering expenses payable by the Company, were approximately \$0.24 million. Aegis Capital Corp. (“Aegis”) acted as the exclusive placement agent in connection with the private placement under a Placement Agent Agreement, dated as of January 27, 2023, between the Company and Aegis, pursuant which Aegis was paid a commission equal to 8.0% of the gross proceeds received by the Company. The warrants were offered and sold in reliance on the exemption from registration provided by Section 4(a)(2) of the Securities Act. The investor also represented that it qualified as an “accredited investor” within the meaning of Rule 501 of Regulation D.

I-1

On February 28, 2023, the Company entered into a license agreement with AnnJi Pharmaceutical Co. Ltd., a Taiwanese company (“AnnJi”), whereby the Company obtained an exclusive license from AnnJi to certain intellectual property rights. Under such license agreement, in exchange for exclusive rights to the licensed intellectual property, the Company will pay an initial cash license fee of \$3.0 million and became obligated to issue 831,618 shares of Common Stock to AnnJi, and then will issue an additional 276,652 shares of Common Stock upon the achievement of a certain clinical study milestone. Such shares were offered and sold in reliance on the exemption from registration provided by Section 4(a)(2) of the Securities Act. AnnJi also represented that it qualified as an “accredited investor” within the meaning of Rule 501 of Regulation D.

Item 16. Exhibits and Financial Statement Schedules

| Exhibit No. | Description | Incorporated by Reference | | | Exhibit No. | Filed herewith |
|---------------------|--|---------------------------|---------------------------|------------------------------------|---------------------|----------------|
| | | Form | File Number | Date | | |
| 3.1 | Third Amended and Restated Certificate of Incorporation of Avenue Therapeutics, Inc. | 8-K | 001-38114 | June 27, 2017 | 3.1 | |
| 3.2 | Certificate of Amendment of the Third Amended and Restated Certificate of Incorporation of Avenue Therapeutics, Inc. | 10-Q | 001-38114 | August 14, 2018 | 3.1 | |
| 3.3 | Certificate of Amendment of the Third Amended and Restated Certificate of Incorporation of Avenue Therapeutics, Inc. | 8-K | 000-38114 | September 22, 2022 | 3.1 | |
| 3.4 | Certificate of Amendment of the Third Amended and Restated Certificate of Incorporation of Avenue Therapeutics, Inc. | 8-K | 000-38114 | February 1, 2023 | 3.1 | |
| 3.5 | Second Amended and Restated Bylaws of Avenue Therapeutics, Inc. | 8-K | 000-38114 | February 10, 2023 | 3.1 | |
| 4.1 | Specimen certificate evidencing shares of Common Stock | 10-12G | 000-55556 | January 12, 2017 | 4.1 | |
| 4.2 | Form of warrant agreement | 10-12G | 000-55556 | January 12, 2017 | 4.2 | |
| 4.3 | Description of Securities of Avenue Therapeutics, Inc. | 10-K | 001-38114 | March 31, 2023 | 4.3 | |
| 4.4 | Form of Warrant | 8-K | 000-38114 | October 12, 2022 | 4.1 | |

| | | | | | | |
|-----------------------|--|--------------------------|----------------------------|----------------------------------|-----------------------|-------------------|
| 4.5 | Form of Pre-funded Warrant | 8-K | 000-38114 | October 12, 2022 | 4.2 | |
| 4.6 | Form of Pre-funded Warrant (Registered Offering) | 8-K | 000-38114 | February 1, 2023 | 10.3 | |
| 4.7 | Form of PIPE Warrant (PIPE) | 8-K | 000-38114 | February 1, 2023 | 10.4 | |
| 5.1 | Opinion of McGuireWoods LLP | | | | | X |
| 10.1 | Asset Transfer and License Agreement between Fortress Biotech, Inc. and Revogenex Ireland Limited dated February 17, 2015* | 10-12G/A | 000-55556 | March 13, 2017 | 10.1 | |
| 10.2 | First Amendment to Asset Transfer and License Agreement between Fortress Biotech, Inc. and Revogenex Ireland Limited dated June 23, 2016 | 10-12G/A | 000-55556 | March 13, 2017 | 10.11 | |
| 10.3 | Second Amendment to Asset Transfer and License Agreement between Fortress Biotech, Inc. and Revogenex Ireland Limited dated May 4, 2017 | S-1/A | 333-217552 | May 22, 2017 | 10.3 | |
| 10.4 | Amended and Restated Founders Agreement between Fortress Biotech, Inc. and Avenue Therapeutics, Inc. dated September 13, 2016 | 10-12G | 000-55556 | January 12, 2017 | 10.2 | |
| 10.5 | Management Services Agreement between Fortress Biotech, Inc. and Avenue Therapeutics, Inc. effective as of February 17, 2015 | 10-12G | 000-55556 | January 12, 2017 | 10.5 | |
| 10.6 | Avenue Therapeutics, Inc. 2015 Incentive Plan | 10-12G | 000-55556 | January 12, 2017 | 10.7 | |
| 10.7 | Consulting Agreement with Dr. Scott A. Reines, dated July 22, 2015 | 10-12G | 000-55556 | January 12, 2017 | 10.8 | |
| 10.8 | First Amendment to Consulting Agreement with Dr. Scott A. Reines, dated January 25, 2016# | 10-12G | 000-55556 | January 12, 2017 | 10.9 | |
| 10.9 | Second Amendment to Consulting Agreement with Dr. Scott A. Reines, dated August 2, 2016# | 10-12G/A | 000-55556 | March 13, 2017 | 10.10 | |
| 10.10 | Third Amendment to Consulting Agreement with Dr. Scott A. Reines, dated February 28, 2017# | 10-12G/A | 000-55556 | March 13, 2017 | 10.12 | |
| 10.11 | Stock Contribution Agreement, dated May 11, 2022, between Avenue Therapeutics, Inc. and Fortress Biotech, Inc. | 10-Q | 001-38114 | August 15, 2022 | 10.1 | |

| | | | | | | |
|-----------------------|---|----------------------|---------------------------|----------------------------------|----------------------|-------------------|
| 10.12 | Underwriting Agreement, dated October 6, 2022, by and between Avenue Therapeutics, Inc. and Aegis Capital Corp. | 8-K | 001-38114 | October 12, 2022 | 1.1 | |
| 10.13 | Warrant Agent Agreement, dated October 6, 2022, by and between Avenue Therapeutics, Inc. and VStock Transfer, LLC | 8-K | 001-38114 | October 12, 2022 | 4.1 | |
| 10.14 | Form of Securities Purchase Agreement (Registered Offering), dated January 27, 2023, by and among Avenue Therapeutics, Inc. and the purchaser party thereto | 8-K | 001-38114 | February 1, 2023 | 10.1 | |
| 10.15 | Form of Securities Purchase Agreement (PIPE), dated January 27, 2023, by and among Avenue Therapeutics, Inc. and the purchaser party thereto | 8-K | 001-38114 | February 1, 2023 | 10.2 | |
| 10.16 | Form of Registration Rights Agreement, dated January 27, 2023, by and among Avenue Therapeutics, Inc. and the purchaser party thereto | 8-K | 001-38114 | February 1, 2023 | 10.5 | |
| 10.17 | Placement Agent Agreement entered into by and between Avenue Therapeutics, Inc. and Aegis Capital Corp., dated January 27, 2023 | 8-K | 001-38114 | February 1, 2023 | 10.7 | |
| 16.1 | Letter from BDO USA, LLP | 8-K | 001-38114 | January 25, 2023 | 16.1 | |
| 21.1 | Subsidiaries of Avenue Therapeutics, Inc. | 10-K | 001-38114 | March 31, 2023 | 21.1 | |
| 23.1 | Consent of Independent Registered Public Accounting Firm, KPMG LLP as to Avenue Therapeutics, Inc., for year ended December 31, 2022 | | | | | X |
| 23.2 | Consent of Independent Registered Public Accounting Firm, BDO USA, LLP as to Avenue Therapeutics, Inc., for year ended December 31, 2021 | | | | | X |
| 23.3 | Consent of Independent Registered Public Accounting Firm, KPMG LLP, as to Baergic Bio, Inc. | | | | | X |

| | | | | | | |
|----------------------|---|--|--|--|--|-------------------|
| 23.4 | Consent of McGuireWoods LLP (included in Exhibit 5.1) | | | | | X |
| 24.1 | Power of Attorney (included in signature page hereto) | | | | | X |
| 107 | Filing Fee Table | | | | | X |

* Subject to a request for confidential treatment.

Management contract or compensatory plan.

Item 17. Undertakings.

The undersigned registrant hereby undertakes:

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

Provided, however, that Paragraphs (i), (ii), and (iii) of this section do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to section 13 or section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in this registration statement,

B. That, for the purpose of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

C. To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

D. That, for the purpose of determining liability under the Securities Act to any purchaser, each prospectus filed pursuant to Rule 424(b) as part of a registration statement relating to an offering, other than registration statements relying on Rule 430B or other than prospectuses filed in reliance on Rule 430A, shall be deemed to be part of and included in the registration statement as of the date it is first used after effectiveness. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such first use, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such date of first use.

E. The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the registrant's annual report pursuant to section 13(a) or section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in this registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

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

SIGNATURES

Pursuant to the requirements of the Securities Act, the Registrant has duly caused this Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in Bay Harbor Islands, Florida, on April 10, 2023.

Avenue Therapeutics, Inc.

By: /s/ Alexandra MacLean
 Name: Alexandra MacLean, M.D.
 Title: Chief Executive Officer

POWER OF ATTORNEY

Each person whose signature appears below constitutes and appoints each of Alexandra MacLean, M.D., and David Jin, acting alone or together with another attorney-in-fact, as his or her true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for such person and in his or her name, place and stead, in any and all capacities, to sign any or all further amendments (including post-effective amendments) to this registration statement (and any additional registration statement related hereto permitted by Rule 462(b) promulgated under the Securities Act, (and all further amendments, including post-effective amendments, thereto)), and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorney-in-fact and agent, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act, this Registration Statement has been signed by the following persons in the capacities and on the dated indicated.

Signature

Title

Date

/s/ Alexandra MacLean

Chief Executive Officer and Director

April 10, 2023

Alexandra MacLean, M.D.

(Principal Executive Officer)

/s/ David Jin

Chief Operating Officer and Interim Chief Financial
Officer

David Jin

*(Principal Financial Officer and Principal Accounting
Officer)*

April 10, 2023

/s/ Jay Kranzler

Jay Kranzler, M.D., Ph.D.

Chairman of the Board

April 10, 2023

/s/ Faith Charles

Faith Charles

Director

April 10, 2023

/s/ E. Garrett Ingram

E. Garrett Ingram

Director

April 10, 2023

/s/ Neil Herskowitz

Neil Herskowitz

Director

April 10, 2023

/s/ Curtis Oltmans

Curtis Oltmans

Director

April 10, 2023

/s/ Lindsay A. Rosenwald

Lindsay A. Rosenwald, M.D.

Director

April 10, 2023



McGuireWoods LLP
 201 North Tryon Street
 Suite 3000
 Charlotte, NC 28202-2146

April 10, 2023

Avenue Therapeutics, Inc.
 1111 Kane Concourse, Suite 301
 Bay Harbor Islands, FL 33154

RE: Registration Statement on Form S-1

Ladies and Gentlemen:

We have acted as counsel to Avenue Therapeutics, Inc., a Delaware corporation (the “Company”), in connection with the Registration Statement on Form S-1 (as amended, the “Registration Statement”) being filed by the Company on the date of this opinion letter with the Securities and Exchange Commission (the “SEC”) under the Securities Act of 1933, as amended (the “Securities Act”). The Registration Statement relates to the registration of the offer and resale by a certain selling stockholder of the Company of 1,940,299 shares of the Company’s Common Stock, par value \$0.0001 per share (the “Securities”) issuable upon the exercise of certain warrants (the “Warrants”) originally issued by us on January 31, 2023 in a transaction exempt from the registration requirements of the Securities Act.

This opinion letter is being furnished in accordance with the requirements of Item 16 of Form S-1 and Item 601(b)(5)(i) of Regulation S-K promulgated under the Securities Act. The Securities are described in the Registration Statement. Capitalized terms used and not defined herein shall have the meanings assigned to them in the Registration Statement.

Documents Reviewed

In connection with this opinion letter, we have examined:

- (a) the Registration Statement, including the exhibits being filed therewith and incorporated by reference therein from previous filings made by the Company with the SEC;
- (b) the prospectus contained in the Registration Statement (the “Prospectus”);
- (c) the Warrants; and
- (d) the Securities Purchase Agreement, dated January 27, 2023, between the Company and the selling stockholder named in the Prospectus (the “PIPE Purchase Agreement”).

In addition, we have examined and relied upon the following:

- (i) a certificate from the corporate secretary of the Company certifying as to (A) true and correct copies of the Third Amended and Restated Certificate of Incorporation of the Company and Second Amended and Restated Bylaws of the Company, each as in effect the date hereof and as amended to date, and (B) the resolutions of the Board of Directors of the Company authorizing (1) the filing of the Registration Statement by the Company; and (2) the Securities issuable by the Company upon exercise of the Warrants;

Atlanta | Austin | Baltimore | Charlotte | Charlottesville | Chicago | Dallas | Houston | Jacksonville | London | Los Angeles - Century City
 Los Angeles - Downtown | New York | Norfolk | Pittsburgh | Raleigh | Richmond | San Francisco | Tysons | Washington, D.C.

Avenue Therapeutics, Inc.
 April 10, 2023
 Page 2 of 3

- (ii) a certificate dated April 10, 2023 issued by the Secretary of State of the State of Delaware, attesting to the corporate status of the Company in the State of Delaware; and

- (iii) originals, or copies identified to our satisfaction as being true copies, of such other records, documents and instruments as we have deemed necessary for the purposes of this opinion letter.

“Applicable Law” means the Delaware General Corporation Law.

Assumptions Underlying Our Opinions

For all purposes of the opinions expressed herein, we have assumed, without independent investigation, the following:

- (a) Factual Matters. To the extent that we have reviewed and relied upon (i) certificates of the Company or authorized representatives thereof, (ii) representations of the Company set forth in the PIPE Purchase Agreement and (iii) certificates and assurances from public officials, all of such certificates, representations and assurances are accurate with regard to factual matters and all official records (including filings with public authorities) are properly indexed and filed and are accurate and complete.

- (b) Signatures. The signatures of individuals who signed the PIPE Purchase Agreement and the Warrants are genuine and (other than those of individuals signing on behalf of the Company at or before the date hereof) authorized.

- (c) Authentic and Conforming Documents. All documents submitted to us as originals are authentic, complete and accurate, and all documents submitted to us as copies conform to authentic original documents.

- (d) Organizational Status, Power and Authority and Legal Capacity of Certain Parties. All parties to the PIPE Purchase Agreement and the Warrants were, as of the date the PIPE Purchase Agreement and Warrants were executed and delivered, validly existing and in good standing in their respective jurisdictions of formation, except

that no such assumption is made as to the Company as of the date hereof. All parties to the PIPE Purchase Agreement and the Warrants had, as of the date the PIPE Purchase Agreement and the Warrants were executed and delivered, the capacity and full power and authority to execute, deliver and perform the PIPE Purchase Agreement, the Warrants and the documents required or permitted to be delivered and performed thereunder. All individuals who signed the PIPE Purchase Agreement and the Warrants had, as of the date the PIPE Purchase Agreement and the Warrants were executed and delivered, the legal capacity to execute the PIPE Purchase Agreement and the Warrants.

(e) Authorization, Execution and Delivery of Subject Document The PIPE Purchase Agreement, the Warrants and the documents required or permitted to be delivered thereunder have been duly authorized by all necessary corporate, limited liability company, business trust, partnership or other action on the part of the parties thereto and have been duly executed and delivered by such parties.

(f) PIPE Purchase Agreement and Warrants Binding on Certain Parties. The PIPE Purchase Agreement, the Warrants and the documents required or permitted to be delivered thereunder were, as of the date the PIPE Purchase Agreement was executed and delivered, valid and binding obligations enforceable against the parties thereto in accordance with their terms, except that no such assumption is made as to the Company.

Avenue Therapeutics, Inc.
April 10, 2023
Page 3 of 3

(g) No Mutual Mistake, Amendments, etc. There has not been any mutual mistake of fact, fraud, duress or undue influence in connection with the issuance of the Securities as contemplated by the Registration Statement, the PIPE Purchase Agreement and the Warrants. There are and will be no oral or written statements or agreements that modify, amend or vary, or purport to modify, amend or vary, any of the terms of the PIPE Purchase Agreement.

(h) Registration. The Registration Statement shall have been declared effective under the Securities Act, and such effectiveness shall not have been terminated or rescinded.

Our Opinions

Based on and subject to the foregoing and the exclusions, qualifications, limitations and other assumptions set forth in this opinion letter, we are of the opinion that the Securities have been duly authorized and, when issued and delivered upon exercise of the Warrants against payment therefor in accordance with the terms of the Warrants, will be validly issued, fully paid and non-assessable.

Our opinions set forth above is limited to the Applicable Law, and we do not express any opinion concerning any other law.

Miscellaneous

The foregoing opinions are being furnished only for the purpose referred to in the first paragraph of this opinion letter. Our opinions are based on statutes, regulations and administrative and judicial interpretations which are subject to change. We undertake no responsibility to update or supplement these opinions subsequent to the effective date of the Registration Statement. Headings in this opinion letter are intended for convenience of reference only and shall not affect its interpretation. We hereby consent to the filing of this opinion as Exhibit 5.1 to the Registration Statement on or about the date hereof, to the incorporation by reference of this opinion of counsel into the Registration Statement and to the reference to our firm in the Prospectus under the caption "Legal Matters." In giving this consent, we do not admit that we are within the category of persons whose consent is required by Section 7 of the Securities Act or the rules and regulations of the SEC promulgated thereunder.

Very truly yours,

/s/ McGuireWoods LLP

McGuireWoods LLP

Consent of Independent Registered Public Accounting Firm

We consent to the use of our report dated March 31, 2023, with respect to the consolidated financial statements of Avenue Therapeutics, Inc., incorporated herein by reference and to the reference to our firm under the heading “Experts” in the prospectus.

/s/ KPMG LLP

New York, New York
April 10, 2023

Consent of Independent Registered Public Accounting Firm

Avenue Therapeutics, Inc.
Bay Harbor Islands, FL

We hereby consent to the incorporation by reference in the Prospectus constituting a part of this Registration Statement of our report dated March 25, 2022, relating to the financial statements of Avenue Therapeutics, Inc. appearing in the Company's Annual Report on Form 10-K for the year ended December 31, 2022. Our report contains an explanatory paragraph regarding the Company's ability to continue as a going concern.

We also consent to the reference to us under the caption "Experts" in the Prospectus.

/s/ BDO USA, LLP

New York, New York

April 10, 2023

Consent of Independent Registered Public Accounting Firm

We consent to the use of our report dated August 31, 2022, with respect to the financial statements of Baergic Bio, Inc., incorporated herein by reference and to the reference to our firm under the heading “Experts” in the prospectus.

/s/ KPMG LLP

New York, New York
April 10, 2023

Calculation of Filing Fee Tables

Form S-1
(Form Type)

Avenue Therapeutics, Inc.
(Exact Name of Registrant as Specified in its Charter)

Table 1: Newly Registered Securities

| Security Type | Security Class Title | Fee Calculation Rule ⁽¹⁾ | Amount Registered ⁽²⁾ | Proposed Maximum Offering Price Per Unit ⁽¹⁾ | Maximum Aggregate Offering Price ⁽¹⁾ | Fee Rate | Amount of Registration Fee |
|-------------------------------|--|-------------------------------------|----------------------------------|---|---|-----------|----------------------------|
| Equity | Common Stock, par value \$0.0001 per share | 457(c) | 1,940,299 ⁽³⁾ | \$ 1.19 ⁽²⁾ | \$ 2,308,955.81 | .00011020 | \$ 254.45 |
| Total Offering Amounts | | | | | \$ 2,308,955.81 | | \$ 254.45 |
| Total Fee Offsets | | | | | | | — |
| Net Fee Due | | | | | | | \$ 254.45 |

(1) Pursuant to Rule 457(c) under the Securities Act, and solely for the purpose of calculating the registration fee, the proposed maximum offering price per share is the average of the high and low prices reported for the registrant's Common Stock quoted on The Nasdaq Capital Market LLC on April 3, 2023.

(2) Pursuant to Rule 416(a) under the Securities Act, this registration statement also covers an indeterminate number of additional shares as may be issuable as a result of stock splits, stock dividends or similar transactions.

(3) Represents 1,940,299 shares of Common Stock issuable upon the exercise of common stock purchase warrants to purchase one share of Common Stock at an exercise price of \$1.55 issued to a certain selling stockholder on January 27, 2023.