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

FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Fiscal Year Ended December 31, 2022

or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the Transition Period from _____ to _____ .

Commission File Number 001-38114

AVENUE THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**47-4113275**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

1111 Kane Concourse, Suite 301, Bay Harbor Islands, FL 33154
(Address of principal executive offices and zip code)

(781) 652-4500
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

(Title of Class)	Trading Symbol(s)	(Name of exchange on which registered)
Common Stock, par value $0.0001 per share	**ATXI**	**Nasdaq Capital Market**

Securities registered pursuant to section 12(g) of the Act: None.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

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	☐	Accelerated filer	☐
Non-accelerated filer	☒	Smaller reporting company	☒
Emerging growth company	☐		

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of the voting stock held by non-affiliates of the registrant the last business day of the registrant's most recently completed second fiscal quarter: $2,946,058.

Indicate the number of shares outstanding of each of the registrant's classes of common stock, as of the latest practicable date.

Class of Common Stock	Outstanding Shares as of March 28, 2023
Common Stock, $0.0001 par value	5,944,149

DOCUMENTS INCORPORATED BY REFERENCE

Part III incorporates information from certain portions of the registrant's definitive proxy statement to be filed with the Securities and Exchange Commission within 120 days after the fiscal year end of December 31, 2022.

AVENUE THERAPEUTICS, INC.
ANNUAL REPORT ON FORM 10-K
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SPECIAL CAUTIONARY NOTICE REGARDING FORWARD-LOOKING STATEMENTS

Certain matters discussed in this report may constitute forward-looking statements for purposes of the Securities Act of 1933, as amended (the "Securities Act"), and the Securities Exchange Act of 1934, as amended (the "Exchange Act"). All statements other than statements of current or historical fact contained in this report, 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," "should," "project," "will," "would" and similar expressions 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 Biotech, Inc. ("Fortress") controls a voting majority of our common stock and has rights to receive significant share grants annually; and

- the risks described under the section titled "Risk Factors" in this Annual Report and in other filings we make with the Securities and Exchange Commission.

The forward-looking statements contained in this report 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 press release, except as required by applicable law. We qualify all of our forward-looking statements by these cautionary statements.

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 in Item 1A, and the other reports and documents that we have filed with the Securities and Exchange Commission ("SEC").

Risks Pertaining to Our Business and Influence

- We currently have no drug products for sale, but we are developing 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 (“DEA”) 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 Biotech, Inc. (“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.

PART I

Item 1. Business

Overview

Avenue Therapeutics, Inc. ("Avenue" or the "Company") is a specialty pharmaceutical company focused on the development and commercialization of 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 February 2023, we announced that 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.

In November 2022, we completed a Share Contribution Agreement, dated May 11, 2022 (the "Share Contribution Agreement") with Fortress Biotech, Inc ("Fortress") to acquire the shares in Baergic Bio, Inc. ("Baergic"), which is developing BAER-101, a novel α2/3–subtype-selective GABA A positive allosteric modulator ("PAM"). As a result, Baergic is a majority-controlled and owned subsidiary company of Avenue.

As used throughout this filing, the words "we", "us" and "our" may refer to Avenue individually or together with our subsidiary, Baergic, each as dictated by context.

We are a majority-controlled subsidiary of Fortress.

Acquisition of Our Product Candidates Under Development

AJ201

In February 2023, we licensed intellectual property rights pertaining to the molecule known as JM17, which actives Nrf1 and Nrf2, enhances androgen receptor degradation and underlies AJ201 from AnnJi Pharmaceutical Co. Ltd. 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 ("ODD") by the U.S. Food and Drug Administration 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 (the "First CRL") from the FDA in October 2020. In February 2021, we resubmitted the NDA for IV Tramadol. The FDA assigned a Prescription Drug User Fee Act ("PDUFA") goal date of April 12, 2021

for the resubmitted NDA for IV Tramadol. On June 14, 2021, we announced that we had received a second Complete Response Letter (the "Second CRL") from the FDA regarding our NDA for IV tramadol. We 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.

We announced on March 8, 2023 that the Company would participate in a Type C meeting with the FDA on March 9, 2023 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 α2/3–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.

Our Strategy

Our primary objective is to establish each of our product candidates as an invaluable part of a treating physician's repertoire of available pharmaceutical options for the treatment of patients with rare and neurologic diseases. The key elements of our strategy include:

- *Develop AJ201 for the treatment of spinal and bulbar muscular atrophy ("SBMA") and potentially other polyglutamine (PolyQ)-related diseases.* In February 2023, we licensed AJ201 for the treatment of SBMA and continue to work with the licensor in conducting the ongoing Phase 1b/2a multi-center trial in the United States that we believe could establish the drug's safety, tolerability, pharmacokinetic, and pharmacodynamic profile.

- *Obtain FDA approval of IV Tramadol for the management of postoperative acute pain.* In December 2019, we submitted an NDA for IV Tramadol and received the First CRL from the FDA in October 2020. In February 2021, we resubmitted the NDA for IV Tramadol. The FDA assigned a PDUFA goal date of April 12, 2021 for the resubmitted NDA for IV Tramadol. On June 14, 2021, we announced that we had received the Second CRL from the FDA regarding our NDA for IV tramadol. We continue to pursue regulatory approval for IV Tramadol and had a Type A meeting with the FDA in July 2021. We submitted a 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 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 an 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. We currently are discussing a potential safety study that may address the FDA's concerns and form the basis for the submission of a complete response to the Second CRL.

- *Develop BAER-101 for treatment of neurologic disorders including epilepsy and acute anxiety.* In November 2022, we acquired Baergic, which has a single asset in development called BAER-101 (formerly known as AZD7325) which has established a safety profile in over 700 patients and has also demonstrated efficacy in several preclinical models that may predict clinical efficacy in new indications.

- *Maintain, expand and protect our intellectual property portfolio.* We intend to expand and protect our intellectual property in the area of rare and neurologic diseases by evaluating potential product candidates for license or other acquisition.

AJ201 and the SBMA Treatment Market

SBMA Background

We are currently focused on developing AJ201 for the treatment of spinal and bulbar muscular atrophy ("SBMA"), also known as Kennedy's Disease.

SBMA is a rare, inherited, X-linked genetic neuromuscular disease primarily affecting men. Onset of the disease is typically in adulthood, between the ages of 30 and 50, and results in significant debilitating symptoms and decreased quality of life issues.

The condition is caused by a polyglutamine expansion in the 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. Although there is a range of cited prevalence rates in the literature, a recent study using genetic analysis to estimated disease prevalence of 1:6,887 males. (Zanovello M *et al. Brain.* 2023; doi:10.1093/brain/awad050).

Currently, there is no FDA approved treatment for SBMA and patients are managed with physical therapy, steroids, and pain management in the United States. Therapies in development focus on the reduction of aggregated mutant androgen receptors and resultant neurotoxicity.

AJ201 Overview

AJ201 is a pleiotropic small molecule that was designed to modify multiple mechanisms including degradation of the abnormal AR protein and stimulation of Nrf1 and Nrf2, which are involved in protecting cells form oxidative stress which can lead to cell death. We believe AJ201 may treat SBMA by enhancing mutant protein degradation and decreasing neuroinflammation.

AJ201 has been granted Orphan Drug Designation by the FDA for SBMA, Huntington's disease, and spinocerebellar ataxia.

Development History and Strategy

Preclinical efficacy data has shown that AJ201: (1) reduces levels and accumulation of the mutant AR protein in mouse muscle tissues; (2) enhances degradation of mutant AR in SBMA patient fibroblasts; and (3) leads to improved motor function in symptomatic animals compared with vehicle control based on a grip test in an SBMA disease mouse model.

In 2021, a Phase 1 single ascending dose and multiple ascending dose study was conducted with AJ201 in healthy volunteers in Australia. A total of 72 subjects were enrolled and none were withdrawn due to safety concerns. The drug was shown to be well tolerated with no serious adverse events and no significant food effect on drug absorption. The drug-proportional exposure was over 40-fold of the dose ranging from 15 mg to 600 mg and drug absorption plateaued above 600 mg. No drug accumulation was seen over repeated daily treatment.

In late 2022, a Phase 1b/2a multicenter double-blind randomized clinical trial was initiated to assess the tolerability of AJ201 in patients with clinically and genetically defined SBMA with a secondary objective of assessing the pharmacokinetics and pharmacodynamics of AJ201 in skeletal muscles. We expect the trial to enroll 20 early SBMA patients 18 years of age or older in the U.S. across six sites including Stanford University, University of California, Irvine, the National Institutes of Health, Mayo Clinic Jacksonville, Mayo Clinic Rochester, and Washington University in St. Louis. The patients will be dosed once daily orally with 600 mg of AJ201 for 12 weeks with a four-week follow-up period.

Tramadol and The U.S. Postoperative Pain Market

Postoperative Pain Market

We are currently focused on developing IV Tramadol for the management of postoperative acute pain. Even though the postoperative pain market is entrenched with low cost, generic pain relievers, we believe that there remains a significant unmet medical need for safer and better-tolerated analgesics.

The major goal in the management of postoperative pain is minimizing the dose of medications to lessen side effects while still providing adequate pain relief for analgesia. Understanding the range of available interventions and considering the type of surgery is essential in order to provide safe and effective pain management. The general consensus among pain management practitioners is that use of more than one modality (i.e., molecules with different mechanisms or with different routes of administration) is optimal for successful postoperative pain management. The most commonly prescribed agents in the immediate postoperative pain market are typically acetaminophen, or APAP, NSAIDS, and opioid analgesics. APAP and NSAIDs are not sufficiently effective as the sole agent for pain management after major surgery in most patients. However, when used in conjunction with opioids, APAP and NSAIDs offer substantial benefits as the quality of analgesia is often improved or enhanced due to their differentiated mechanism of action.

Traditional opioids offer safe and effective postoperative pain control and can be used in combination with other agents and techniques. However, the side effects of opioids, such as morphine, include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression. Physical dependence and addiction are clinical concerns that may prevent proper prescribing and, in turn, inadequate pain management. Less common side effects include delayed gastric emptying, hyperalgesia, immunologic and hormonal dysfunction, muscle rigidity, and myoclonus. Importantly, they are Schedule II opioids (per DEA classification) and carry a high abuse potential.

Tramadol

Tramadol, a synthetic dual-acting opioid, is a centrally acting analgesic with weak opioid agonist properties. It also works via the inhibition of serotonin and noradrenaline re-uptake and blocking nociceptive impulses at the spinal level. These opioid and non-opioid modes of action are synergistic, essentially providing “multimodal therapy” with the use of a single drug. Tramadol is also commonly combined with APAP or NSAIDS in clinical practice. Tramadol has a well-established efficacy and safety profile and has been used throughout the world for more than 30 years. In the United States, tramadol is approved and marketed as an oral agent indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Tramadol was first approved in the United States in 1995, under the trade name Ultram® immediate release tablet (Ortho-McNeil-Janssen). Ultracet®, a combination product containing tramadol and acetaminophen, is also marketed in the United States (Ortho-McNeil-Janssen). According to Symphony Health Solutions, approximately 30 million scripts for tramadol and tramadol-containing drugs were filled in retail pharmacies in the United States in 2020.

Tramadol has low potential for abuse and addiction and is currently classified by the DEA as a Schedule IV controlled substance. For comparison, other opioids which have a high potential for abuse, including meperidine, morphine, hydromorphone and oxycodone, are all classified as Schedule II controlled substances.

The clinical trials from our development program are summarized below:

- Lu, L., et al. Comparing the Pharmacokinetics of 2 Novel Intravenous Tramadol Dosing Regimens to Oral Tramadol: A Randomized 3-Arm Crossover Study. *Clinical Pharmacology in Drug Development*. October 2019.

- Minkowitz, H., et al. Intravenous Tramadol is Effective in the Management of Postoperative Pain Following Abdominoplasty: A Three-Arm Randomized Placebo- and Active-Controlled Trial. *Drugs in R&D*. May 2020.

- Minkowitz, H., et al. IV Tramadol – A New Treatment Option for Management of Post-Operative Pain in the U.S.: An Open-Label, Single-Arm, Safety Trial Including Various Types of Surgery. *Journal of Pain Research*. May 2020.

- Singla, N., et al. Efficacy and Safety of Intravenously Administered Tramadol in Patients with Moderate to Severe Pain Following Bunionectomy: A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study. *Pain and Therapy.* July 2020.

According to the Drug Enforcement Administration (DEA) definition, substances classified as Schedule II have "a high potential for abuse, with use potentially leading to severe psychological or physical dependence" and substances classified as Schedule IV are "drugs with lower potential for abuse than Schedule II and consist of preparations containing limited quantities of certain narcotics."

The table below summarizes the available intravenous analgesic options in postoperative pain management currently available in the United States.

Available Classes	Pain Levels	Common Limitations & Contraindications
IV narcotics	Moderate to severe	Strong sedation
		Respiratory depression
		Constipation
		Risk of dependence
IV NSAIDS	Mild to severe	Post-op bleeding risk
		GI side effects
		Renal impairment
IV acetaminophen	Mild to moderate	Hepatic impairment

Advantages of IV Tramadol

Parenteral tramadol is approved and used for the management of postoperative acute pain throughout much of the world. Parenteral formulations include IV, intramuscular, or IM, and subcutaneous, or SC, formulations. During the 10-year period from 2010 to 2019, approximately 370 million doses of parenteral tramadol were used in Europe, according to data from IQVIA (a 3rd party data provider). There is no parenteral formulation currently approved in the United States.

We believe that IV Tramadol, if approved, can fill the unmet need in the post-surgical setting and could be an effective alternative to traditional opioids but carry a lower potential for abuse because tramadol is a Schedule IV opioid in the U.S. We believe that the introduction of an IV formulation of tramadol in the United States will address many of the shortcomings of other opioid agonists, and APAP, and NSAIDs, all of which are currently used in the postoperative setting. IV Tramadol's potential advantages compared to current standard-of-care agents, along with the known efficacy, safety and tolerability profile for oral tramadol support the use of IV Tramadol in this setting. We believe that the risks associated with the use of IV Tramadol will be benign compared to other opioids, and consistent with that of the currently marketed oral tramadol products. Consequently, with the industry trend toward multimodal therapy and away from Schedule II narcotics, if approved, IV Tramadol's unique profile could position it to become an invaluable part of a treating physician's repertoire of available pharmaceutical options in the management of postoperative pain.

We administered IV Tramadol over approximately 15 minutes in our Phase 3 trials. We believe that our method of administration of IV Tramadol may provide significant benefits such as reduced side effects, compared to previously approved methods of administration of IV Tramadol in Europe, which is typically accomplished via a slow push over 2 to 3 minutes. In addition, our IV Tramadol dosing regimen produces a similar Cmax (maximal blood level) and AUC (overall systemic exposure) to those of oral tramadol at steady state, which we believe ensures an easy transition from IV to oral therapy in the post-surgical setting.

Based on the trials done in Europe and on the data generated with oral tramadol, we believe that IV Tramadol, if approved, will be an attractive option for physicians who treat postoperative pain in the U.S., due to the following attributes:

- As an established analgesic, tramadol has documented efficacy and safety and physicians are already familiar with the drug.
- As a Schedule IV controlled substance, tramadol has less potential for addiction and abuse than other narcotics widely prescribed in the post-surgical setting. In the current environment where the opioid epidemic is a recognized problem in the United States and there are increasing restrictions on Schedule II opioids, a Schedule IV opioid such as tramadol may become a more attractive option.
- Importantly, there is a step-down therapy available for IV Tramadol. Patients are transitioned to oral therapy when they are discharged from the hospital or when they can tolerate oral medicine. Our IV Tramadol dosing regimen provides a similar PK profile to that of oral tramadol at steady state to ensure a smooth step-down process.

Clinical Development History

Revogenex, the previous Sponsor and Licensor, completed multiple nonclinical PK and toxicology studies in dogs, a Phase 1 dose proportionality study and a thorough QT/QTc ("TQT") study of IV Tramadol in healthy volunteers, or the TQT Study. The dose proportionality study was designed to compare maximum exposure and cumulative exposures of IV Tramadol to that of oral tramadol, and to assess the dose proportionality of IV Tramadol in healthy adult volunteers. The TQT Study was done to evaluate whether IV Tramadol has the potential to affect the "corrected QT interval", or QTc, in healthy volunteers. The QTc represents electrical depolarization and repolarization of the heart ventricles. A lengthened QTc is a marker for the potential of ventricular arrhythmias. The results of these studies are consistent with tramadol's known toxicology profile, pharmacokinetics and pharmacology.

PK Study for IV Tramadol

In general, Phase 2 clinical trials include initial proof-of-concept efficacy studies, dose-finding studies, and initial safety assessments in the target (i.e., to-be-treated) population. We did not conduct Phase 2 clinical trials for IV Tramadol because tramadol is a known analgesic, and oral tramadol is labeled "for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate" in the United States. Instead, we completed pharmacokinetic ("PK") simulations and conducted a pharmacokinetic and safety study in healthy volunteers, in order to select a Phase 3 dose and dosing regimen designed to achieve exposure to tramadol similar to that provided by oral tramadol. In 2016, we completed a PK study for IV Tramadol in healthy volunteers. A PK study generally involves dosing an experimental medicine in healthy volunteers and taking a series of blood measurements from the study participants to understand how the body handles the drug. A PK study provides information on important parameters such as systemic exposure, maximal and minimal levels of drug concentration in the blood and their time courses. The PK study we conducted was used to select a dose and dosing regimen of IV Tramadol that achieves similar exposure to that provided by oral tramadol at steady state.

The PK study was designed as a three-way cross over study in 18 healthy volunteers. Each subject in the study served as his/her own control and received oral tramadol as well as two different doses of IV Tramadol. Based on the results of the PK study, we decided to use a 50 mg dose in our pivotal Phase 3 program.

Our Clinical Development Strategy for IV Tramadol

At our EOP2 meeting with FDA, we discussed Phase 3 program requirements for IV Tramadol and confirmed the key elements of the Phase 3 program design. We conducted two pivotal Phase 3 trials to evaluate the safety and efficacy of IV Tramadol, and one additional safety study. All three trials enrolled patients who required IV analgesia following surgery. Over 1,000 patients were enrolled in the Phase 3 program. We believe that the design of our Phase 3 program is consistent with the design of Phase 3 programs for other analgesics being developed.

Postoperative pain following bunionectomy (orthopedic surgery model). The first Phase 3 trial was conducted in patients undergoing bunionectomy surgery, which is considered an orthopedic surgical model. 409 patients were randomized and treated in a 1:1:1 ratio to one of two doses of IV Tramadol, or placebo, for 48 hours. The primary efficacy endpoint was Sum of Pain Intensity Difference over 48 hours (SPID 48), which is a measure of the overall effectiveness of the drug in reducing pain intensity during the 48-hour period. This trial commenced in the third quarter of 2017. In May 2018, we announced the trial met its primary endpoint and all key secondary endpoints.

Postoperative pain following abdominoplasty (soft tissue model). The second Phase 3 safety and efficacy trial was conducted in patients undergoing abdominoplasty surgery, which is considered a soft-tissue surgical model. 370 patients were randomized and treated in a 3:3:2 ratio to IV Tramadol, placebo or a standard-of-care comparator arm. The primary efficacy endpoint was Sum of Pain Intensity Difference over 24 hours (SPID 24). The trial commenced in December 2018. In June 2019, we announced the trial met its primary endpoint and all key secondary endpoints.

Open-label safety study. We initiated the safety study in December 2017 and ran this study concurrently with the two Phase 3 trials. 251 patients were enrolled in the safety study, which had an open label, single arm design. We completed this study in May 2019 and the results showed that IV Tramadol was well-tolerated in multiple surgical models with a side effect profile consistent with known pharmacology.

License Agreement with Revogenex Ireland Ltd.

Effective as of February 17, 2015, Fortress obtained a worldwide (with the exception of Canada, Central America and South America with respect to 50 mg and 100 mg IV Tramadol HCl injections) exclusive license to make, market and sell IV Tramadol pursuant to an agreement with Revogenex, a privately held company in Dublin, Ireland, or the License Agreement. Under the terms of the License Agreement, Fortress paid Revogenex an up-front licensing fee of $2.0 million upon execution and an additional $1.0 million on June 17, 2015. A $1.0 million milestone payment was due upon NDA submission in December 2019 which was incurred by us. There is also an additional milestone totaling $3.0 million due upon the FDA approval of IV Tramadol. Additional high single-digit to low double-digit royalty payments on net sales of licensed products are due. Royalties will be paid on a product-by-product and country-by-country basis until the expiration in each country of the valid patent claim. In return, Fortress obtained the exclusive worldwide rights to three U.S. patents related to the "Intravenous Administration of Tramadol": U.S. Patent No. 8,895,622 (the '622 patent), which issued on November 25, 2014; U.S. Patent No. 9,561,195 (the '195 patent), which issued on February 7, 2017; and U.S. Patent No. 9,566,253 (the '253 patent), which issued on February 14, 2017 (all with the exception of Canada, Central America and South America with respect to 50 mg and 100 mg IV Tramadol HCl injections). Additionally, Fortress acquired the rights to an open U.S. Investigational New Drug Application pertaining to IV Tramadol, as well as all supporting documentation and relevant correspondence with the FDA. Further, under the License Agreement, Fortress assumed the rights and obligations of Revogenex under its current manufacturing agreement with Zaklady Farmaceutyczne Polpharma (Polpharma), or the Manufacturing Agreement. Fortress transferred all its rights and obligations under the License Agreement and the Manufacturing Agreement to us pursuant to an Asset Transfer Agreement, dated as of May 13, 2015.

The License Agreement will terminate on a product-by-product and country-by-country basis upon the expiration of the last licensed patent right, unless the agreement is earlier terminated. In addition to standard early termination provisions, the License Agreement may also be terminated early by: (i) Revogenex if the FDA does not issue an approval or otherwise issues a "not approvable" notice for the NDA within 27 months after the NDA has been filed with the FDA (December 2019), although this termination right will be tolled if we are using commercial reasonable efforts in our negotiations with the FDA for approval and if we receive a "not approvable" notice (October 2020), we will have a 15 month period to correct any issues and re-submit the NDA for approval, (ii) us if we reasonably determine prior to NDA approval that the development of IV Tramadol is not economically viable, or (iii) either Revogenex or us (provided we are using or have used commercially reasonable efforts to commercialize IV Tramadol) if, after the third anniversary date of the commercial launch, we fail to achieve annual net sales with respect to IV Tramadol of at least $20 million in any given calendar year, with certain exceptions.

BAER-101 and the Addressable Market

BAER-101 Overview and Strategy

BAER-101 (formerly known as AZD7325) is a novel selective oral GABA-A α2 and α3 PAM. Modulators of GABA-A receptors (GABA-ARs) have entered a new age in their clinical development with multiple assets moving forward since the 2019 U.S. FDA approval of brexanolone (Zulresso®). These compounds are being developed for a host of therapeutic indications including epilepsy, anxiety, pain, depression, and other disease states. BAER-101 is a small molecule potentiator of GABA-ARs with oral bioavailability that preferentially activates α2- and α3-containing GABA-ARs.

Preclinical data have substantiated the efficacy of BAER-101 as a novel anxiolytic and antiepileptic with potential for also treating Fragile X Syndrome. Consistent with its selectivity over α1-preferring GABA-ARs, BAER-101 may have a reduced propensity to produce sedation and memory impairment.

BAER-101 has demonstrated efficacy in several preclinical models that may predict efficacy in patients. BAER-101 produced potent anxiolytic-like effects in rodents, anticonvulsant activity in certain rodent seizure models, efficacy in rodent models of Dravet syndrome and in a rodent model of Fragile X syndrome. Studies in rodents have also demonstrated good tolerability, with minimal ability to induce motor and memory impairment, characteristic effects of non α-selective GABA-AR potentiators like the benzodiazepine ("BDZ") diazepam. EEG power analysis also differentiated BAER-101 from compounds like the BDZ lorazepam. Physical dependence and abuse liability of BAER-101 are also reduced in model systems compared to non-selective GABA-AR modulators.

We plan to validate BAER-101's efficacy in highly predictive preclinical models to inform the optimal path forward for the Phase 1b clinical trial(s) that we intend to initiate in 2023.

Diseases Currently Treated with Nonselective GABA-A Drugs: Benzodiazepines

Epilepsy Background

Epilepsy is a chronic disease that manifests as recurrent unprovoked seizures from abnormal electrical discharge in the brain. An epilepsy diagnosis requires at least 2 unprovoked seizures.

The current standard of care treatment involves use of one or more anti-epileptic drugs ("AED"). Side effects of approved therapies include dizziness, nausea, headache, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor. Even with the availability of approved drugs, 30% of patients do not achieve seizure control with two or more AEDs and these patients are characterized as drug-resistant. The consequences of poorly controlled epilepsy can be quite severe and include shortened lifespan, excessive bodily injury, neuropsychological and psychiatric impairment, and social disability.

Benzodiazepines are a class of AED that are used to treat seizures (convulsions). The use of benzodiazepines for a chronic disease such as epilepsy is limited by the side effect profile including drowsiness, confusion, dizziness, impaired coordination, increased risk of falls and accidents, and depression. More serious side effects include memory problems and behavioral changes — such as increased risk taking, delirium, and risk of dependence.

Studies have shown that people with seizures have a deficit in GABA neurotransmission. GABA, a major inhibitory neurotransmitter, inhibits the activity of nerves that could initiate the seizure. Benzodiazepines mainly work by affecting the gamma amino-butyric acid (GABA) neurotransmitters in the brain. Specifically, benzodiazepines enhance the activity of GABA by binding to its receptor, and opening its chloride channel, enabling release of GABA, resulting in anticonvulsant activity.

Benzodiazepines act non-selectively by enhancing the inhibitory effects of gamma-amino butyric acid (GABA) at GABA-A receptors containing either an α1, α2, α3, or α5 subunit. The field has progressed with the development of selective GABA-A receptor modulators that preferentially target one or more receptor subunits and BAER-101 is such a modulator. BAER-101 is selective for the α2, α3 receptor subunits an, as a result we believe it should provide an anti-convulsant effect while limiting the side effects associated with the α1 receptor.

Acute Anxiety Background

Panic disorder is a common form of an acute anxiety disorder manifesting as frequent panic attacks unrelated to specific situations. Panic attacks involve sudden, intense episodes of apprehension, terror, feelings of impending doom and intense urge to flee, with symptoms reaching peak intensity within ten minutes. Patients can end up presenting to the emergency room simulating physical symptoms which can include labored breathing, heart palpitations, nausea, upset stomach, chest pain, feelings of choking and smothering, dizziness, sweating, lightheadedness, chills, heat sensations, and trembling. Other symptoms may include depersonalization, derealization, and fears of mental illness, losing control, or dying.

Panic disorder is treated with a combination of cognitive behavioral therapy and anxiolytics (drugs that reduce anxiety). These drugs include the following classes: benzodiazepines, tricyclics, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Side effects can be problematic with existing medications especially with benzodiazepines, that have the potential for symptom exacerbation and abuse.

BAER-101 and AZD7325 Development History

BAER-101 (AZD7325) has been studied in various preclinical studies demonstrating:

- Selective mechanism of action through in vitro studies: high affinity interaction with GABA-ARs containing α1, α2, or α3 subunits and much lower affinity for α5-containing GABA-ARs. Despite interacting with α1, α2 and α3, in functional assays, BAER-101 selectively potentiates α2 and α3 containing GABA-ARs significantly more than those containing α1.

- Anti-convulsant effects through in vivo models: Pilot studies were carried out with mice to establish the anticonvulsant potential of BAER-101. In these studies (n=4), mice were dosed with BAER-101 and then given a convulsant stimulus after 0.25, 0.5, 1, 2, or 4 h post dosing. Mice were given BAER-101 by the intraperitoneal (i.p.) route at 10 mg/kg and by the oral (p.o.) route at 30 mg/kg. The following convulsant stimuli were assessed: maximal electroshock, pentylenetetrazol, and 6Hz corneal stimulation. BAER-101 reduced convulsions by 33% in the maximal electroshock test in one experiment, by 25% in the 6Hz assay, and 75% in the pentylenetetrazol test. There was sedation at 30 mg/kg in some mice in only one of the studies conducted.

- Anxiolytic effects through in vivo models: BAER-101 was tested in three different rodent models and exhibited efficacy: the punished responding model (PR) the rat fear potentiated startle (FPS) model, and the elevated maze model (EM).

- Reduced in vivo side effect profile through animal models: in vitro profile translates to a non-sedative anxiolytic profile in vivo, as characterized in multiple rat models of sedation and anxiety. Non-clinical studies in rat and primate models of cognition and abuse liability demonstrate that BAER-101 has a reduced side effect profile in these domains as well when compared to benzodiazepines. The safety profile of BAER-101 results in robust margins between predicted maximum clinical exposures for efficacy versus the exposures noted to cause toxicity in the most sensitive species.

A total of 722 male and female subjects have been exposed to BAER-101 in clinical trials and the drug has an established safety profile across multiple clinical studies. Studies completed to date include a single ascending dose (SAD) study, a multiple ascending dose (MAD) study, a Japanese SAD study, a 11C-flumazenil-labeled PET study, an exploratory study specifically designed to address cognition and sedation, a study to evaluate drug abuse potential, a study exploring BAER-101's cytochrome P450 (CYP) induction potential, a study investigating the co-administration of BAER-101 with an oral contraceptive (OC), and two Phase 2 efficacy studies in patients with generalized anxiety disorder (GAD), all performed by AstraZeneca. BAER-101 has been administered as a single dose up to 100 mg and repeated doses up to 50 mg administered once daily (QD) for 7 days or 15 mg twice daily (BID) for 28 days. Cincinnati Children's Hospital Medical Center has also completed an investigator-initiated pilot trial in patients with Fragile X Syndrome.

Competition

The pharmaceutical industry is characterized by rapidly advancing technologies, intense competition and a strong emphasis of proprietary products. We face competition and potential competition from a number of sources, including pharmaceutical and biotechnology companies, generic drug companies, drug delivery companies and academic and research institutions. In addition, companies that are active in different but related fields represent substantial competition for us. Many of our competitors have significantly greater capital resources, larger research and development staffs and facilities and greater experience in drug development, regulation, manufacturing and marketing than we do. These organizations also compete with us to recruit qualified personnel, attract partners for joint ventures or other collaborations, and license technologies that are competitive with ours. To compete successfully in this industry, we must identify novel and unique drugs or methods of treatment and then complete the development of those drugs as treatments before our competitors do so.

We believe that IV Tramadol, if approved, will compete with a number of opioid and non-opioid drugs that are currently available for the management of acute pain or in development. The most commonly used opioids in the postoperative and acute pain settings are morphine, hydromorphone and fentanyl. In 2020, the FDA also approved OLINVYK (oliceridine), an intravenous opioid agonist for the management of moderate to severe acute pain in adults, where the pain is severe enough to require an intravenous opioid and for whom alternative treatments are inadequate. The non-opioid drugs used in this setting include Ofirmev (IV acetaminophen) and IV formulations of NSAIDs such as Dyloject (diclofenac), Toradol (ketorolac), Anjeso (meloxicam) and Caldolor (ibuprofen). In addition, we also expect to compete with agents such as Exparel (bupivacaine lipsome injectable suspension), Zynrelef (bupivacaine and meloxicam) and Xaracoll (bupivacaine implant).

In addition to approved products, there are a number of product candidates in development for the management of acute pain. In addition to reformulations and fixed-dose combination products of already available therapies, there are also several novel agents in clinical development such as NTM-001 (Neumentum, Inc.) and CA-008 (Concentric Analgesics, Inc.).

We believe that BAER-101, if approved, will compete with a number of selective and non-selective GABA A receptor agonists. The most commonly used therapies for anxiety and epilepsy are benzodiazepines. Commonly prescribed benzodiazepine therapies are Valium (diazepam), Ativan (lorazepam), Alepam (oxazepam), Alodorm (nitrazepam), Euhypnos (temazepam), Xanax (alprazolam), Clonazepam (klonopin). There are other selective GABA A receptor agonists in clinical development such as darigabat (Cerevel), ENX101 (Engrail Therapeutics), and SAN711 (Saniona).

We believe that AJ201, if approved, will compete with a number of programs targeting various neurologic pathways. There are no FDA approved therapies to treat SBMA. Product candidates in development for the treatment of SBMA include NIDO-361 (Nido Biosciences) and AAV gene therapy targeting mutant androgen receptor (University of Pennsylvania). In Japan, Leuprorelin (Takeda) is approved for the treatment of SBMA, but is not approved outside of Japan.

Intellectual Property and Patents

General

Our goal is to obtain, maintain and enforce patent protection for our proprietary technologies, including methods of treatment, to preserve our trade secrets, and to operate without infringing on the proprietary rights of other parties, both in the United States and in other countries. Our policy is to actively seek to obtain, where appropriate, the broadest intellectual property protection possible for our product candidates, proprietary information and proprietary technology through a combination of contractual arrangements and patents in the United States.

Patents and other proprietary rights are crucial to the development of our business. We will be able to protect our proprietary technologies from unauthorized use by third parties only to the extent that our proprietary rights are covered by valid and enforceable patents, are supported by regulatory exclusivity or are effectively maintained as trade secrets. We have several patents and patent applications related to our proprietary technology, but we cannot guarantee the scope of protection of the issued patents, or that such patents will survive a validity or enforceability challenge, or that any of the pending patent applications will issue as patents.

Generally, patent applications in the United States are maintained in secrecy for a period of 18 months or more. The patent positions of biotechnology and pharmaceutical companies are highly uncertain and involve complex legal and factual questions. Therefore, we cannot predict the breadth of claims allowed in biotechnology and pharmaceutical patents, or their enforceability. To date, there has been no consistent policy regarding the breadth of claims allowed in biotechnology patents. Third parties or competitors may challenge or circumvent our patents or patent applications, if issued. If our competitors prepare and file patent applications in the United States that claim technology also claimed by us, we may have to participate in interference proceedings declared by the USPTO to determine priority of invention, which could result in substantial cost, even if the eventual outcome is favorable to us. In the case of inventorship contests relating to patent applications filed on or after March 16, 2013, we may have to participate in derivation proceedings initiated at the Patent Trial and Appeal Board (PTAB), which could also result in substantial cost. Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that before we commercialize any of our products, any related patent may expire or remain in existence for only a short period following commercialization, thus reducing any advantage of the patent. However, the life of a patent covering a product that has been subject to regulatory approval may have the ability be extended through the patent restoration program, although any such extension could still be minimal.

If a patent is issued to a third party containing one or more preclusive or conflicting claims, and those claims are ultimately determined to be valid and enforceable, we may be required to obtain a license under such patent or to develop or obtain alternative technology, neither of which may be possible. In the event of litigation involving a third-party claim, an adverse outcome in the litigation could subject us to significant liabilities to such third party, require us to seek a license for the disputed rights from such third party, and/or require us to cease use of the technology. Moreover, our breach of an existing license or failure to obtain a license to technology required to commercialize our products may seriously harm our business. We also may need to commence litigation to enforce any patents issued to us or to determine the scope and validity of third party proprietary rights. Litigation would involve substantial costs.

IV Tramadol

Pursuant to the License Agreement described above, we have exclusive, worldwide commercialization rights to all Revogenex patents, including patent applications, divisionals, continuations, and continuations-in-part, that are directed to IV tramadol (with the exception of Canada, Central America, or South America with respect to 50 mg and 100 mg IV tramadol HCl injections). Currently, this includes U.S. Patent No. 8,895,622 (“the ’622 patent”), U.S. Patent No. 9,561,195 (“the ’195 patent”), U.S. Patent 9,566,253 (“the ’253 patent”), U.S. Patent No. 9,962,343 (“the ’343 patent”), U.S. Patent No. 10,406,122 (“the ’122 patent”), U.S. Patent No. 9,693,949 (“the ’949 patent”), U.S. Patent 9,968,551 (“the ’551 patent”), U.S. Patent No. 9,980,900 (“the ’900 patent”), U.S. Patent No. 10,022,321 (“the ’321 patent”), U.S. Patent No. 10,537,521 (“the ’521 patent”), U.S. Patent No. 10,624,842 (“the ’842 patent”), U.S. Patent No. 10,751,279 (the ‘279 patent), U.S. Patent No. 10,729,644 (the ‘644 patent), U.S. Patent No. 10,646,433 (“the ‘433 patent”), U.S. Patent No. 10,617,635 (“the ‘635 patent”), U.S. Patent No. 10,729,645 (”the ‘645 patent”), U.S. Patent No. 10,751,277 (“the ‘277 patent”) and U.S. Patent No. 10,751,278 (“the ‘278 patent”), and any related patent applications or future patents, including divisionals, continuations, and continuations-in-part.

The ’622 patent is directed to and claims methods of: treating pain by administering a therapeutically effective dose of tramadol intravenously over a time period from 10 minutes to about 45 minutes (i.e., the rate of IV Tramadol administration); treating pain in humans by intravenously administering tramadol in solution at a range of concentrations over the same time period; treating acute pain in humans by administering IV Tramadol over 10 to 30 minutes, such that at least one side effect is reduced; and treating acute postoperative pain by administering tramadol to a human patient intra-operatively at wound closure, or from first demand of analgesia postoperatively, intravenously over a time period from 10 to 30 minutes, in conjunction with administering further tramadol doses post-operatively and administering a different intravenous opioid analgesic which is not tramadol. Further claims of the ’622 patent are directed to various effective doses, including 50 mg. These methods of treatment may provide significant benefits (e.g., reduced side effects) over previously approved methods of administration of IV Tramadol, in which the dose was typically accomplished over a two to three-minute period. Additional claims of the ’622 patent focus on the intravenous administration of tramadol over 15 (±2) minutes, which represents the preferred method of administration that we will be pursuing in obtaining approval of our product through the FDA. The ’622 patent further describes and claims pharmacokinetic properties of our proprietary method of treatment (e.g., Tmax, Cmax and AUC), which are different from the previously achieved pharmacokinetics of prior IV tramadol formulations, such as Tramal® solution for injection (available outside the U.S.). This patent is scheduled to expire on October 20, 2032, absent possible regulatory patent term extensions.

In view of additional prior art discovered after the issuance of the ’622 patent, we have focused efforts on obtaining further patent coverage for the technology. Pursuant to the License Agreement, we have exclusive commercialization rights to all continuation patent filings of the ’622 patent. As a first step, we have prosecuted further claims in multiple continuation patent applications of the ’622 patent, in which extensive searches were conducted and all information known to be material to patentability was brought to the attention of the USPTO. The goal was to obtain further patent claims which patentably differentiate over the prior art. To date, our efforts have resulted in the issuance of the ’195 patent, which issued from U.S. Application Serial No. 14/550,279 on February 7, 2017; the ’253 patent, which issued from U.S. Application Serial No. 14/713,775 on February 14, 2017; the ’343 patent, which issued from U.S. Application Serial No. 14/550,279 on May 8, 2018; and the ’122 patent, which issued from U.S Application Serial No. 15/972,684 on September 10, 2019; all of which are entitled “Intravenous Administration of Tramadol,” and all of which contain the same disclosure (specification) as that of the ’622 patent. The ’195, ’253, ’343 and ’122 patents are scheduled to expire on the same day as the expiration of the ’622 patent (October 20, 2032 absent possible regulatory patent term extensions).

The ’253 patent includes claims directed to a method of treating moderate to severe acute pain in a human patient by a dose of about 50 mg of IV Tramadol over a time period from 10 minutes to 20 minutes and administering further doses of tramadol at two to six-hour time intervals (each dose being administered intravenously over the same time period).

The ’343 patent includes claims directed to similar subject matter but varies from the ’253 patent in that it specifically claims treating acute post-operative pain. There is also a continuation patent application pending with the USPTO.

The ’195 patent includes claims directed to a method of treating moderate to severe acute pain by administering to a human patient a dose of about 50 mg of IV Tramadol over 10 to 20 minutes, and administering further doses of IV Tramadol at two to six hour time intervals to treat pain in said patient, (each dose administered over 10 to 20 minutes), such that the Cmax does not exceed the Cmax of 100 mg oral tramadol administered every six hours for nine doses. The term Cmax refers to the maximum plasma concentration of tramadol achieved during a dosing interval. The claims of the ’195 patent therefore further focus on a goal of the technology — that the blood plasma levels of tramadol resulting from our 50 mg intravenous dose to a patient would not be significantly greater than the blood plasma level of the blood plasma levels of tramadol that are already routinely experienced by patients in the United States who are administered oral doses of 100 mg tramadol. Tramadol hydrochloride is approved in the United States for oral administration in an amount from 50 mg to 100 mg administered every four to six hours, not to exceed 400 mg/day.

The ’122 patent includes claims directed to a method of treating moderate to severe acute pain or acute post-operative pain by administering to a human patient undergoing an operation a dose of about 50 mg of tramadol at about 2 to about 6 hour time intervals for at least about 48 hours to treat pain in said patient, wherein each dose of tramadol is administered intravenously over a time period from 10 minutes to 20 minutes, such that the patient is treated for acute postoperative pain. Further claims call for at least one dose of tramadol to be administered over 15 (±2) minutes.

The ’253, ’195, ’343 and ’122 patents include further claims to the treatment method, including also administering one or more doses of an IV opioid analgesic that is not tramadol as rescue medicine to the patient to treat breakthrough pain. The claims are further directed to the use of the treatment method for postoperative pain, and claims in the ’195, ’343, and ’122 patents are also directed to the treatment method resulting in a reduction in a side-effect associated with tramadol therapy selected from nausea, vomiting, or both.

The ’278 and ’277 patents are directed to the treatment method, for example, where acute pain is treated.

Other patents are directed to tramadol doses other than about 50 mg. For example, the patents include the ’279 patent and the ’433 patent (about 60 mg tramadol), and the ’521 patent and the ’321 patent (about 25 mg tramadol).

The ’645, ’644, and ’635 patents are directed to various aspects of the treatment method wherein tramadol is co-administered with another analgesic: ketorolac (the ’645 patent), another analgesic selected from NSAIDs, acetaminophen, and another opioid (the ’644 patent), or acetaminophen (the ’635 patent).

We believe that the administration of, e.g., a 50 mg IV Tramadol dose over the prolonged time interval is efficacious and also may advantageously lead to a lower incidence of side effects and increased drug tolerability. Additionally, we believe that the claims of these patents patentably differentiate over all prior art that we are aware of and which was made of record with the USPTO.

The License Agreement also grants us the exclusive commercialization rights to the ’949 patent and any related patent applications or future patents, including divisionals, continuations, and continuations-in-part. The ’949 patent is directed to an IV Tramadol dosing regimen and issued on July 4, 2017. This new patent describes and claims a dosing regimen in which our IV Tramadol product is dosed to a human patient(s) for treating acute pain in a manner such that the plasma levels obtained (including but not limited to Cmax and AUC) are very similar to treatment with a 100 mg oral dose of tramadol hydrochloride to a human patient(s) every six hours at steady state. This is accomplished by intravenously administering a first dose of tramadol 50 mg to a human patient; then intravenously administering a second dose of tramadol 50 mg about 2 hours after the first dose; intravenously administering a third dose of tramadol 50 mg about 2 hours after the second dose; and thereafter intravenously administering doses of tramadol 50 mg at dosage intervals of about 4 hours. It is believed that this dosing regimen may provide advantages over the commercially available oral doing regimen, and further allows the patient to be stepped down from the IV Tramadol dosing regimen to an oral dosing regimen with less concern about deleterious effects which might occur from a switch from IV to oral analgesic medicine (e.g., as would be the case where the switch to an oral version of the drug provides a much different Cmax and AUC than the IV dose provides at steady state). This new dosing regimen is the result of considerable experimentation by us, and a prior art search has not revealed any similar dosing regimen being used or published with respect to IV Tramadol infusions. The patent term of the ’949 patent is scheduled to expire on May 24, 2036, absent possible regulatory patent term extensions.

A continuation of the ’949 patent issued as the ’551 patent on May 18, 2018, claiming the same dosing regimen except that it includes claims that specify that the mean Cmax after the third administered dose of tramadol is similar to the mean Cmax at steady-state for a dosing regimen of 100 mg tramadol HCl administered orally every 6 hours, and/or specifies pharmacokinetic parameters for Cmax and/or AUC at steady-state. The ’551 patent is scheduled to expire on the same day as the ’949 patent (May 24, 2036, absent possible regulatory patent term extensions).

The ’900 patent (a continuation-in-part of the ’949 patent) issued on May 29, 2018 and is directed to the same dosing regimen, except that it includes claims that specify the pharmacokinetic parameters after the third administered dose of tramadol. Further continuation patent applications are pending for (i) the 50 mg dosing regimen to human patients experiencing acute pain or acute post-operative pain; (ii) the 50 mg dosing regimen directed to administering a first dose of tramadol 50 mg to a human patient and thereafter intravenously administering additional doses of tramadol to the human patient(s) in an amount of about 50 mg tramadol at dosage intervals of about 4 hours, except that a second dose is intravenously administered as a loading dose at a shortened interval as compared to the dosage interval of about 4 hours, and (iii) administering the 50 mg dosing regimen as described with an NSAID as well. The ’900 patent is scheduled to expire on the same day as the ’949 patent (May 24, 2036, absent possible regulatory patent term extensions).

The License Agreement also grants us the exclusive commercialization rights to continuation applications of the ’949, ’551, and ’900 patents (and related applications) that are currently pending at the USPTO. This includes, but is not limited to, U.S. Application Serial No. 15/976,503 (“the ’503 application”), a continuation of the ’551 patent and filed on May 10, 2018; U.S. Application Serial No. 16/223,522 (“the ’522 application”), a continuation of the ’199 application and filed on December 18, 2018; U.S. Application Serial No. 15/986,199 (“the ’199 application”), a continuation of the ’900 patent and filed on May 22, 2018; and U.S. Application Serial No. 16/223,556 (“the ’556 application”), a continuation of the ’503 application and filed on December 18, 2018. The ’503, ’522, and ’199 applications are directed to various dosing regimens for intravenous administration of a 50 mg dose of tramadol. The ’556 application is directed to various dosing regimens for intravenous administration of a 60 mg dose of tramadol.

The License Agreement further grants us exclusive commercialization rights to new patents/patent applications pending with the USPTO directed to the intravenous administration of tramadol co-administered with other analgesics. Currently, these patent applications include U.S. Application Serial No. 16/269,213 (“the ’213 application”, now the ’279 patent), a continuation of the ’556

application and filed February 6, 2019; U.S. Application Serial No. 16/269,124 ("the '124 application"; now U.S. Patent No. 10,729,644), a continuation of the '522 application and filed on February 6, 2019; U.S. Application Serial No. 16/375,363 ("the '363 application", now the '635 patent), a continuation of the '213 application and filed on April 4, 2019 (now U.S. Patent No. 10,751,279); and U.S. Application Serial No. 16/376,382 ("the '382 application", now the '645 patent), a continuation of the '213 application and filed on April 5, 2019. The '213 application is directed to intravenously administering a first dose of 60 mg of tramadol, later administering doses every 6 hours (except for the second dose, which is a loading dose administered in a shorter time period), and also administering another analgesic. The '124 application (now the '644 patent) is similar, but it claims a dosage of 50 mg. The '363 application is also similar to the '213 application, in that it claims 60 mg, but it varies in that it specifies acetaminophen as the other analgesic. The '382 application is similar to the '124 application, in that it claims 50 mg, but it varies in that it specifies ketorolac as the other analgesic.

The License Agreement also grants us the exclusive commercialization rights to the '321 patent, which is directed to an IV Tramadol dosing regimen and issued on July 17, 2018. This new patent describes and claims a dosing regimen in which our IV Tramadol product is dosed to a human patient(s) for treating acute pain by intravenously administering a first dose of tramadol 25 mg to a human patient; then intravenously administering a second dose of tramadol 25 mg about 2 hours after the first dose; intravenously administering a third dose of tramadol 25 mg about 2 hours after the second dose; and thereafter intravenously administering doses of tramadol 25 mg at dosage intervals of about 4 hours. The '321 patent is scheduled to expire on April 13, 2037, absent possible regulatory patent term extensions.

A continuation of the '321 patent issued as the '521 patent on January 21, 2020, claiming the same dosage as the '321 patent (25 mg), but over dosing intervals of about 4 hours, where the second dose is intravenously administered as a loading dose at a shortened interval as compared to the interval of about 4 hours. It further claims this method of treatment, where the at least one side effect, selected from nausea, vomiting, and seizure, is reduced. The '521 patent is scheduled to expire on the same day as the '321 patent (April 13, 2037, absent possible regulatory patent term extensions).

With the exception of 50 mg and 100 mg dosages of IV tramadol HCl in Canada, Central America, and South America, the License Agreement also grants us the exclusive commercialization rights to certain foreign patents and patent applications, including PCT applications. With the exception of the territory constraint listed above, we have the exclusive commercialization rights to PCT Application No. US/2012/033304 and any related patents or patent applications.

In sum, we believe that our patent filings will prevent third parties from marketing a generic version of our product without infringing claims of the patent(s) we are seeking. Further, we have conducted clearance searches of U.S. issued and foreign patents, and have not identified any bars to the commercialization of our tramadol technology.

BAER-101

In December 2019, Baergic licensed intellectual property related to BAER-101 (formerly known as AZD7325) from AstraZeneca Plc ("AZ") and Cincinnati Children's Hospital Medical Center ("CCHMC") relating to AZD7325 including four issued U.S. patents and related foreign patents. Two of the issued U.S. patents claim the compound itself, related cinnoline compounds, and pharmaceutical preparations thereof and related foreign patents including Canada, China, France, Germany, Italy, Japan, Spain, Sweden, Switzerland, and United Kingdom. Two additional US patents claim methods of use of the compound as it relates to an orphan disease. The compound-related patents may first begin to expire as early as December 2026 and the method of use patents may first begin to expire as early as 2036.

AJ201

In February 2023, we licensed intellectual property rights pertaining to the molecule known as JM17 which underlies the final product form AJ201. The intellectual property licensed includes issued patents in the US relating to the compound itself, and methods of use for treating various medical conditions associated with the androgen receptor. The compound-related patent may first begin to expire as early as 2029 and the method patent as early as 2028. There is also an additional issued patent relating to methods of treating various neurodegenerative disorders which may first begin to expire in 2040.

Other Intellectual Property Rights

We depend upon trademarks, trade secrets, and continuing technological advances to develop and maintain our competitive position. We also depend upon the skills, knowledge and experience of our scientific and technical personnel, as well as that of our advisors,

consultants and other contractors. This knowledge and experience we call "know-how." To help protect our proprietary know-how which is not patentable, and for inventions for which patents may be difficult to enforce, we rely on trade secret protection and confidentiality agreements to protect our interests. To this end, we require all employees, scientific advisors, consultants, collaborators and other contractors, upon commencement of a relationship with us, to enter into confidentiality agreements, which prohibit the disclosure of confidential information and, in the case of parties other than our research and development collaborators, require disclosure and assignment to us of the ideas, developments, discoveries and inventions important to our business. These agreements are designed to protect our proprietary information and to grant us ownership of technologies that are developed in connection with their relationship with us. These agreements may not, however, provide protection for our trade secrets in the event of unauthorized disclosure of such information.

Supply and Manufacturing

The chemical name for tramadol hydrochloride is cis-2-[(dimethyl amino) methyl]-1-(3-methyoxyphenyl) cyclohexanol hydrochloride. Unless otherwise specified, the term tramadol refers to the racemic mixture of the (±) cis isomers. IV Tramadol (Tramadol Hydrochloride Injection) is a sterile solution formulation of tramadol HCl 50 mg/1 mL, for IV administration. Each unit of IV Tramadol consists of glass ampoules of 50 mg of tramadol HCl and sodium acetate as buffering agent in 1 mL of water for injection. The final drug product is stable at room temperature.

We do not own or operate manufacturing facilities for the production of our product candidates, nor do we have plans to develop or own manufacturing operations in the foreseeable future. Currently, we have one manufacturer, Polpharma, who subcontracts several activities to another manufacturer, to provide us clinical and commercial supply of IV Tramadol in accordance with current Good Manufacturing Practice (CGMP) requirements. We also may plan to qualify a backup manufacturer. We will be obligated to purchase a minimum amount of final packaged drug product from our current manufacturer over the course of five years commencing upon the approval of our NDA for IV Tramadol. We will pay a fixed per dose unit fee to our current manufacturer in addition to a low single digit royalty on net sales revenue and a milestone payment amount of $2.0 million upon FDA approval of IV Tramadol.

We and our manufacturers, as well as their key subcontractors, are and will be subject to extensive government regulation in connection with the manufacture of any pharmaceutical product, including ongoing periodic and unannounced inspections by the FDA, the DEA and corresponding state, European and other foreign agencies to ensure strict compliance with CGMPs and other applicable state, federal and foreign regulations. We do not have control over third party manufacturers' compliance with these regulations and standards, other than through contractual obligations and audit oversight. If they are deemed out of compliance with CGMPs, product recalls could result, inventory could be destroyed, production could be stopped and supplies could be delayed or otherwise disrupted.

If we need to change manufacturers after commercialization, the FDA and some corresponding foreign regulatory agencies must approve these new manufacturers in advance, which will involve testing and additional inspections to ensure compliance with CGMPs and other FDA regulations and standards and may require significant lead times and delay. Furthermore, switching manufacturers may be difficult because the number of potential manufacturers is limited. It may be difficult or impossible for us to find a replacement manufacturer quickly or on terms acceptable to us, or at all.

Government and Industry Regulations

Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of products such as those we are developing.

U.S. Drug Development

In the United States, the FDA regulates drugs under the FDCA, and its implementing regulations. Since IV Tramadol is an opioid, such drugs are also regulated by the DEA as controlled substances under the Controlled Substances Act, even at the drug development stage. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approval and maintaining subsequent compliance with applicable federal, state and local statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during product development, the approval process or after approval may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, voluntary product recalls or market withdrawals, product seizures, total or partial suspension of production or distribution injunctions,

fines, consent decrees, refusals of government contracts, restitution, disgorgement or civil and criminal penalties. Any regulatory, compliance or enforcement action by any agency or judicial enforcement action could have a material adverse effect on our products, or our Company. If we fail to manufacture IV Tramadol in sufficient quantities and at acceptable quality and pricing levels, fail to comply with additional DEA requirements related to controlled substances, or fail to fully comply with CGMP regulations, we may face delays in the commercialization of IV Tramadol or be unable to meet market demand, and may be unable to generate potential revenues.

Our product candidates must be approved by the FDA through one of FDA's available drug approval processes before they may be legally marketed in the United States – (1) an NDA submitted under section 505(b)(1) of the FDCA; (2) an abbreviated new drug application ("ANDA") under section 505(j); or (3) a new drug application submitted under section 505(b)(2) of the FDCA (505(b)(2) application). We have already submitted our first 505(b)(2) application and intend to utilize the 505(b)(2) regulatory approval pathway for any additional product candidates. Development and approval of drugs generally involves the following:

- Submission to the FDA of an IND, which must become effective before clinical trials involving humans may begin;
- Approval by an independent institutional review board, or IRB, or ethics committee at each clinical trial site before a trial may be initiated at that site;
- Performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations and other good clinical practices, or GCPs;
- Submission of an application (NDA, ANDA or 505(b)(2)) to the FDA;
- The FDA's decision within 60 days of its receipt of an NDA to accept it for filing and review;
- Satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with CGMPs and assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- Possible FDA audit of the clinical trial sites that generated the data in support of the NDA; and
- FDA review and approval of the NDA.

The nonclinical testing, clinical trials and review process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all. The data required to support an NDA are generated in two distinct developmental stages: nonclinical and clinical. The nonclinical development stage generally involves synthesizing the active component, developing the formulation and control procedures and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which may support subsequent clinical testing in humans. In the case of documentation to support a 505(b)(2) NDA, this nonclinical data may be referenced in literature or the FDA's previous findings of safety and efficacy for a listed drug. The sponsor must submit the results of the nonclinical studies, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans, and must become effective before clinical trials may begin. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the IND on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

The clinical stage of development involves the administration of the product candidate to healthy volunteers and patients under the supervision of qualified investigators, generally physicians not employed by or under the sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent IRB for each institution where the trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each subject or his or her legal representative and must monitor the clinical trial until completed.

Clinical Trials

Clinical trials are generally conducted in three sequential phases, known as Phase 1, Phase 2 and Phase 3, and may overlap.

- Phase 1 clinical trials generally involve a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacology, side effect tolerability and safety of the drug.

- Phase 2 clinical trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamics information is collected, possible adverse effects and safety risks are identified and a preliminary evaluation of efficacy is conducted.

- Phase 3 clinical trials generally involve large numbers of patients at multiple sites and are designed to provide the data necessary to demonstrate the product candidate's safety and effectiveness for its intended use, establish its overall benefit/risk relationship, and provide an adequate basis for approval.

Post-approval trials, sometimes referred to as Phase 4, may be conducted after initial marketing approval. These trials are used to gain additional experience from the management of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

Before approval, progress reports detailing the results of the clinical trials, among other information, must be submitted at least annually to the FDA, and written IND safety reports must be submitted to the FDA and investigators for serious and unexpected suspected adverse events, findings from other studies suggesting a significant risk to humans exposed to the same or similar drugs, findings from animal or *in vitro* testing suggesting a significant risk to humans, and any clinically important rate increase of a serious suspected adverse reaction compared to that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the trial is not being conducted in accordance with the IRB's requirements or the use of the drug raises any safety concerns. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the sponsor, known as a data safety monitoring board or committee. Depending on its charter, this group may determine whether a trial may move forward at designated check points based on access to certain data from the trial.

There are also requirements governing the reporting of ongoing clinical trials and completed trial results to public registries. Sponsors of certain clinical trials of FDA-regulated products are required to register and disclose specified clinical trial information, which is publicly available at *www.clinicaltrials.gov*. Information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed until the new product or new indication being studied has been approved. However, there are evolving rules and increasing requirements for publication of all trial-related information, and it is possible that data and other information from trials involving drugs that never garner approval could require disclosure in the future.

Concurrent with clinical trials, companies usually develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing it in commercial quantities in accordance with CGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate, and, among other things, a drug manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug product. Appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

NDA and FDA Review Process

The results of nonclinical studies and clinical trials, together with other detailed information, including extensive information on manufacturing and drug composition and proposed labeling, are submitted to the FDA in the form of an NDA requesting approval to market the drug for one or more specified indications. The FDA reviews an NDA to determine, among other things, whether a drug is safe and effective for its intended use and whether the product is being manufactured in accordance with CGMPs to assure and preserve

the product's identity, strength, quality and purity. FDA approval of an NDA must be obtained before a drug may be legally marketed in the United States.

Under the PDUFA as amended in 2017, each NDA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's current fee schedule for fiscal year (FY) 2023, effective through September 30, 2023, the user fee for an application requiring clinical data, such as an NDA, is $3,242,026. Clinical data, as interpreted by the FDA to assess fees under PDUFA, include (1) study reports or literature reports of what are explicitly or implicitly represented by the applicant to be adequate and well-controlled trials for safety or effectiveness or (2) reports of comparative activity (other than bioequivalence and bioavailability studies), immunogenicity, or efficacy, where those reports are necessary to support a claim of comparable clinical effect. The term does not include bioequivalence and bioavailability studies submitted in support of an NDA. PDUFA also imposes an annual Prescription Drug Program Fee ($393,933 per approved prescription drug product for FY 2023) for establishments named as the applicant in a human drug application. An establishment is not to be assessed more than five (5) prescription drug program fees in a given fiscal year. Fee waivers or reductions are available in certain circumstances, including waiver of the application fee for the first application filed by a small business.

The FDA performs an administrative review of an NDA before accepting it for filing and may request additional information rather than accepting the applications. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth scientific and technical review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months from the filing date in which to complete its initial review of a standard NDA and respond to the applicant, and six months from the filing date for an NDA designated for priority review. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with CGMPs. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with CGMP requirements and adequate to assure consistent production of the product to specifications. The FDA may also audit data from clinical trials to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation regarding whether the application should be approved and, if so, under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers them carefully when making decisions. NDAs submitted under Section 505(b)(2) are typically not referred to an Advisory Panel for consideration unless new safety information is revealed in the review cycle. The FDA likely will re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the applicant during the review process. The review and evaluation of an NDA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

After the FDA evaluates an NDA, it will issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application will not be approved in its present form. A Complete Response Letter usually describes the specific deficiencies in the NDA identified by the FDA, and may require additional clinical data, such as an additional pivotal Phase 3 clinical trial, and other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information are submitted, the FDA may decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive, and the FDA may interpret data differently than the sponsor interprets the same data.

There is no assurance that the FDA will approve a product candidate for marketing, and the sponsor may encounter significant difficulties or costs during the review process. If a product receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling, or it may condition approval on changes to the proposed labeling. The FDA also may condition approval on the development of adequate controls and specifications for manufacturing and a commitment to conduct post-marketing testing and surveillance to monitor the potential effects of approved products. For example, the FDA may require Phase 4 trials designed to further assess a drug's safety and efficacy.

The FDA may also place other conditions on approval including the requirement for a risk evaluation and mitigation strategy, or REMS, to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Marketing approval may be withdrawn for non-compliance with regulatory requirements or if problems occur following initial marketing.

Section 505(b)(2) Regulatory Approval Pathway

Section 505(b)(2) was added to the Act by the Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments). Section 505(b)(2) of the FDCA provides an alternate regulatory pathway for approval of a new drug by allowing the FDA to rely on data not developed by the applicant. Specifically, Section 505(b)(2) permits the submission of an NDA where one or more of the investigations relied upon by the applicant for approval was not conducted by or for the applicant and for which the applicant has not obtained a right of reference. The applicant may rely upon published literature and/or the FDA's findings of safety and effectiveness for an approved drug already on the market. Approval or submission of a 505(b)(2) application, like those for abbreviated new drugs, or ANDAs, may be delayed because of patent and/or exclusivity rights that apply to the previously approved drug.

Under the 505(b)(2) regulatory approval pathway, the applicant may reduce some of the burdens of developing a full clinical program by relying on investigations not conducted by the applicant and for which the applicant has not obtained a right of reference, such as prior investigations involving the listed drug. In such cases, some clinical trials may not be required or may be otherwise limited.

A 505(b)(2) application may be submitted for a new chemical entity (NCE), when some part of the data necessary for approval is derived from studies not conducted by or for the applicant and when the applicant has not obtained a right of reference. Such data are typically derived from published studies, rather than FDA's previous findings of safety and effectiveness of a previously approved drug. For changes to a previously approved drug however, an applicant may rely on the FDA's finding of safety and effectiveness of the approved drug, coupled with information needed to support the change from the approved drug, such as new studies conducted by the applicant or published data. When based on an approved drug, the 505(b)(2) drug may be approved for all of the indications permitted for the approved drug, as well as any other indication supported by additional data.

Section 505(b)(2) applications also may be entitled to marketing exclusivity if supported by appropriate data and information. As discussed in more detail below, three-year new data exclusivity may be granted to the 505(b)(2) application if one or more clinical investigations conducted in support of the application, other than bioavailability/bioequivalence studies, were essential to the approval and conducted or sponsored by the applicant. Five years of marketing exclusivity may be granted if the application is for an NCE, and pediatric exclusivity is likewise available.

Orange Book Listing and Paragraph IV Certification

For NDA submissions, including 505(b)(2) applications, applicants are required to list with the FDA certain patents with claims that cover the applicant's product. Upon approval, each of the patents listed in the application is published in *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly referred to as the Orange Book. Any applicant who subsequently files an ANDA or a 505(b)(2) application that references a drug listed in the Orange Book must certify to the FDA that (1) no patent information on the drug product that is the subject of the application has been submitted to the FDA; (2) such patent has expired; (3) the date on which such patent expires; or (4) such patent is invalid or will not be infringed upon by the manufacture, use or sale of the drug product for which the application is submitted. This last certification is known as a Paragraph IV certification.

If an applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the holder of the NDA for the approved drug and the patent owner once the application has been accepted for filing by the FDA. The NDA holder or patent owner may then initiate a patent infringement lawsuit in response to notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification prevents the FDA from approving the ANDA or 505(b)(2) application until the earlier of 30 months from the date of the lawsuit, the applicant's successful defense of the suit, or expiration of the patent.

Pediatric Information

Under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation in which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers.

The Food and Drug Administration Safety and Innovation Act, or FDASIA, requires that a sponsor who is planning to submit an NDA for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or PSP, within 60 days of an end-of-Phase 2 meeting or, if there is no such meeting, as early as practicable before the initiation of the Phase 3 or Phase 2/3 trial. The initial PSP must include an outline of the pediatric trial(s) that the sponsor plans to conduct, including objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such information and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric trials. The FDA and the sponsor must reach an agreement on the PSP, but the sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials and other clinical development programs.

Post-Marketing Requirements

Following approval, the company and the new product are subject to continuing regulation by the FDA, which include monitoring and recordkeeping activities, reporting of adverse experiences and complying with promotion and advertising requirements, which include prohibitions on the promotion of the drugs for unapproved, or "off-label" uses. Although physicians may prescribe legally available drugs for off-label treatments, manufacturers may not promote such non-FDA approved uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use on an on-going basis. Further, if there are any modifications to the drug, including changes to indications, labeling, or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a supplemental NDA or new NDA, which may require the applicant to develop additional data or conduct additional nonclinical studies or clinical trials.

The FDA regulations require that products be manufactured in specific approved facilities and in accordance with CGMPs. These regulations require, among other things, quality control and quality assurance, the maintenance of records and documentation and the obligation to investigate and correct any deviations from CGMPs. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies, and are subject to periodic, unannounced inspections by the FDA and certain state agencies for compliance with CGMPs and other laws. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with CGMPs. The discovery of violative conditions, including failure to conform to CGMPs, could result in enforcement actions, and the discovery of problems with a product after approval may result in restrictions on a product, manufacturer or holder of an approved NDA, including voluntary recalls and product seizures.

Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, untitled or warning letters from the FDA, mandated corrections to advertising or communications to doctors and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. New government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

U.S. Marketing Exclusivity

The FDCA provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA, for a drug product that contains a previously approved NCE if new clinical investigations, other than bioavailability/bioequivalence studies, were essential to the application's approval (*e.g.*, for new indications, dosages or strengths of an existing drug). This three-year exclusivity for new data covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication. Furthermore, this exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and efficacy.

Pediatric exclusivity is another type of regulatory market exclusivity in the United States, which, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protections or patent term, may be granted based on the voluntary completion of a pediatric trial in accordance with an FDA-issued "Written Request." The FDA issues a written request for pediatric clinical trials before approval of an NDA only where it determines that information relating to the use of a drug in a pediatric population, or part of the pediatric population, may produce health benefits in that population.

DEA Regulation

Because IV Tramadol is subject to the Controlled Substances Act (CSA) we must comply with various statutory requirements set forth by the CSA, as amended, and its implementing regulations as enforced by the DEA. The CSA imposes various registration, record-keeping and reporting requirements, procurement and manufacturing quotas, labeling and packaging requirements, security controls, prescription and order form requirements and restrictions on prescription refills for certain kinds of pharmaceutical products. A principal factor for determining the particular requirements of the CSA applicable to a product, if any, is its actual or potential abuse profile, which is classified into a DEA schedule. A product may be listed as a Schedule I, II, III, IV or V controlled substance, with Schedule I presenting the highest perceived risk of abuse and Schedule V presenting the least. For example, Schedule I controlled substances have no currently accepted medical use in treatment in the United States and a lack of accepted safety for use under medical supervision. The active ingredient in IV Tramadol is classified as a Schedule IV controlled substance.

Annual registration is required for any facility that manufactures, distributes, dispenses, imports or exports any controlled substance. The registration is specific to the particular location, activity and controlled substance schedule. For example, separate registrations are needed for import and manufacturing, and each registration will specify which schedules of controlled substances are authorized. Similarly, separate registrations are also required for separate facilities.

The DEA typically inspects a facility to review its security measures prior to issuing a registration and on a periodic basis. Security requirements vary by controlled substance schedule, with the most stringent requirements applying to Schedule I and Schedule II controlled substances and less stringent requirements for Schedules III, IV, and V. Required security measures include background checks on employees and physical control of inventory through measures such as vaults and inventory reconciliations. Records must be maintained for the handling of all controlled substances, and periodic reports made to the DEA. Reports must also be made for thefts or losses of any controlled substance, and to obtain authorization to destroy any controlled substance.

In addition, a DEA quota system controls and limits the availability and production of controlled substances in Schedule I or II. Distributions of any Schedule I or II controlled substance must also be accompanied by special order forms, with copies provided to the DEA. Because the active ingredient in IV Tramadol is currently regulated as a Schedule IV controlled substances, it will not be subject to the DEA's production and procurement quota scheme.

To enforce these requirements, the DEA conducts periodic inspections of registered establishments that handle controlled substances. Failure to maintain compliance with applicable requirements, particularly as manifested in loss or diversion, can result in administrative, civil or criminal enforcement action. The DEA may seek civil penalties, refuse to renew necessary registrations or initiate administrative proceedings to revoke those registrations. In some circumstances, violations could result in criminal proceedings.

In addition to federal scheduling, some drugs may be subject to state-controlled substance regulation and thus more extensive requirements than those determined by the DEA and FDA.

Other Healthcare Laws and Compliance Requirements

Manufacturing, sales, promotion and other activities following product approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the U.S. Department of Justice, the DEA, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments.

We will also be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy

regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- The federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either (1) the referral of an individual to a person for furnishing any item or service for which payment is available under a federal health care program, or (2) the purchase, lease, order or recommendation thereof of any good, facility, service or item for which payment is available under a federal health care program;

- The False Claims Act and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment from the federal government or making or using, or causing to be made or used, a false record or statement material to a false or fraudulent claim;

- The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program, obtaining money or property of the health care benefit program through false representations or knowingly and willingly falsifying, concealing or covering up a material fact, making false statements or using or making any false or fraudulent document in connection with the delivery of, or payment for, health care benefits or services;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information;

- The provision under the ACA commonly referred to as the Sunshine Act, which requires applicable manufacturers of covered drugs, devices, biologics and medical supplies to track and annually report to CMS payments and other transfers of value provided to physicians and teaching hospitals and certain ownership and investment interests held by physicians or their immediate family members in applicable manufacturers and group purchasing organizations; and

- State law equivalents of each of the above federal laws, such as the Anti-Kickback Statute and False Claims Act, and state laws concerning security and privacy of health care information, which may differ in substance and application from state-to-state thereby complicating compliance efforts.

The ACA broadened the reach of the fraud and abuse laws by, among other things, amending the intent requirement of the federal Anti-Kickback Statute and the applicable criminal healthcare fraud statutes contained within 42 U.S.C. Section 1320a-7b. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the ACA provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act or the civil monetary penalties statute. Many states have adopted laws similar to the federal Anti-Kickback Statute, some of which apply to the referral of patients for healthcare items or services reimbursed by any source, not only the Medicare and Medicaid programs.

As noted above, the federal False Claims Act prohibits anyone from, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment from federal programs, including Medicare and Medicaid. Although we would not submit claims directly to payors, manufacturers can be held liable under these laws if they are deemed to "cause" the submission of false or fraudulent claims by, for example, providing inaccurate billing or coding information to customers. In addition, our future activities relating to the reporting of wholesaler or estimated retail prices for our products, the reporting of prices used to calculate Medicaid rebate information and other information affecting federal, state, and third-party reimbursement for our products, and the sale and marketing of our products are subject to scrutiny under this law. For example, pharmaceutical companies have been prosecuted under the federal False Claims Act in connection with their off-label promotion of drugs. Penalties for such violations could include three times the actual damages sustained by the government, mandatory civil penalties between $10,781 and $21,563 for each separate false claim, exclusion from participation in federal healthcare programs, and the potential implication of various federal criminal statutes. Private individuals also have the ability to bring actions under the federal False Claims Act, or *qui tam* actions, and certain states have enacted laws based on the federal False Claims Act.

Pharmaceutical Coverage, Pricing and Reimbursement

In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third party payors, including government health administrative authorities, managed care providers, private health insurers and other organizations. Third party payors are increasingly examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy, and, accordingly, significant uncertainty exists as to the reimbursement status of newly approved therapeutics. Adequate third-party reimbursement may not be available for our products to enable us to realize an appropriate return on our investment in research and product development. We are unable to predict the future course of federal or state health care legislation and regulations, including any changes, repeal, or judicial invalidation of some or all of the provisions of the Affordable Care Act. The Affordable Care Act and further changes in the law or regulatory framework could have a material adverse effect on our business.

International Regulation

In addition to regulations in the United States, there are a variety of foreign regulations governing clinical trials and commercial sales and distribution of any product candidates. The approval process varies from country to country, and the time may be longer or shorter than that required for FDA approval.

Employees

As of December 31, 2022, we had 2 full-time employees. None of our employees are represented by a labor union and we consider our employee relations to be good.

Corporate Information

Avenue Therapeutics, Inc. was incorporated in Delaware in 2015. Our executive offices are located at 111 Kane Concourse, Suite 301 Bay Harbor Islands, Florida 33154. Our telephone number is (781) 652-4500, and our email address is info@avenuetx.com.

We maintain a website with the address www.avenuetx.com. We make available free of charge through our Internet website our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K, and any amendments to these reports, as soon as reasonably practicable after we electronically file such material with, or furnish such material to, the SEC. We are not including the information on our website as a part of, nor incorporating it by reference into, this report. Additionally, the SEC maintains a website that contains annual, quarterly, and current reports, proxy statements, and other information that issuers (including us) file electronically with the SEC. The SEC's website address is http://www.sec.gov.

Item 1A. Risk Factors

Our business, results of operations and financial condition and the industry in which we operate are subject to various risks. You should carefully consider the risks described below, in addition to the other information contained in this Form 10-K, before making an investment decision. The risks and uncertainties described below are not the only ones we face. Additional risks not presently known to us or other factors not perceived by us to present significant risks to our business at this time also may impair our business operations.

Risks Pertaining to Our Business and Industry

We currently have no drug products for sale, but we are developing three drug product candidates, IV Tramadol, BAER-101 and AJ201. We are dependent on the success of our product candidates, and cannot guarantee that these product candidates will receive regulatory approval or be successfully commercialized.

Our business success depends on our ability to obtain regulatory approval to successfully commercialize, market and sell our product candidates, and any significant delays in obtaining approval to commercialize, market and sell our product candidates will have a substantial adverse impact on our business and financial condition.

If the applications for any of our product candidates are approved, our ability to generate revenues from such product candidates will depend on our ability to:

- establish and maintain agreements with our contract manufacturers, wholesalers, distributors and group purchasing organizations on commercially reasonable terms;
- obtain sufficient quantities of the our product candidates from qualified third-party manufacturers that manufacture in accordance with Current Good Manufacturing Practices (CGMP) requirements, as required to meet commercial demand at launch and thereafter;
- hire, train, deploy and support our sales force;
- create market demand for our products through our own marketing and sales activities, and any other arrangements to promote this product candidates we may later establish;
- conduct such marketing and sales activities in a manner that is compliant with federal and state laws, including restrictions on off-label promotion and anti-kickback requirements;
- obtain and maintain government and private payer reimbursement for our product; and
- maintain patent protection and regulatory exclusivity for our product candidates.

We may not receive regulatory approval for our product candidates, or their approvals may be delayed, which would have a material adverse effect on our business and financial condition.

Our product candidates and other future product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to premarket approval and comprehensive regulation by the FDA, DEA and other regulatory agencies in the United States. Failure to obtain marketing approval for our product candidates will prevent us from commercializing our product candidates. We have not received approval to market our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in conducting preclinical and clinical studies and filing and supporting the applications necessary to gain marketing approvals and expect to rely on third party contract research organizations as well as consultants and vendors to assist us in the process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities.

Our product candidates must meet FDA's standards for safety and efficacy, but may be determined not to be effective, to be only moderately effective, to not be safe for use in its intended population, or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if approval is granted at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in the regulatory review process for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical studies or clinical trials. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

If we experience delays in obtaining approval or if we fail to obtain approval of any of our product candidates or any future product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenue will be materially impaired, thereby negatively impacting our business, financial condition and results of operations.

In addition, even if we were to obtain approval, the approval of the indication for any of our product candidates by such regulatory authorities may, among other things, be more limited than we request. Such regulatory authorities may not approve the price we intend to charge for our product, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. These regulatory authorities may also require the label to contain warnings, contraindications, or precautions that limit the commercialization of that product. Our third-party suppliers may be subject to inspections by the FDA that identifies deficiencies in their manufacturing facilities and concludes they are not operating in compliance with CGMP requirements, which in turn, may force us to identify, qualify and rely upon additional suppliers. Any of these scenarios could compromise the commercial prospects for our product candidates, or any future product candidates.

If serious adverse or unacceptable side effects are identified during the development of our product candidates, we may need to abandon or limit our development of some of our product candidates.

If our product candidates or future product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. In our industry, many compounds that initially showed promise in early-stage testing have later been found to cause undesirable side effects that prevented further development of the compound. In the event that our preclinical or clinical trials reveal a high and unacceptable severity and prevalence of side effects, our trials could be delayed, suspended or terminated and the FDA or comparable foreign regulatory authorities could order us to cease further development or deny approval of our product candidates or future product candidates for any or all targeted indications. The FDA could also issue a letter requesting additional data or information prior to making a final decision regarding whether or not to approve a product candidate. The number of requests for additional data or information issued by the FDA in recent years has increased, and resulted in substantial delays in the approval of several new drugs. Undesirable side effects caused by our product candidates or future product candidates could also result in the inclusion of serious risk information in our product labeling, application of burdensome post-market requirements, or the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, and in turn prevent us from commercializing and generating revenues from the sale of our product candidates. Drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial and could result in potential product liability claims.

For example, some of the adverse events observed in the IV Tramadol clinical trials completed to date include nausea, dizziness, drowsiness, tiredness, sweating, vomiting, dry mouth, somnolence and hypotension. With respect to BAER-101, some of the adverse events observed in clinical trials completed to-date include dizziness, somnolence, headache, and euphoric mood. With respect to AJ201, some of the adverse events observed in clinical trials completed to-date include nausea, diarrhea, headache, and abdominal distension.

Additionally, if one or more of our current or future product candidates receives marketing approval, and we or others later identify undesirable side effects caused by this product, a number of potentially significant negative consequences could result, including:

- regulatory authorities may require the addition of serious risk-related labeling statements, specific warnings, precautions, or contraindication;
- regulatory authorities may suspend or withdraw their approval of the product, or require the suspension of manufacturing, or the recall of the product from the market;
- regulatory authorities may require implementation of burdensome post-market risk mitigation strategies and practices;
- we may be required to change the way the product is administered, conduct additional clinical trials or change the labeling of the product; or
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining marketing approval and market acceptance of our product candidates or future product candidates or could substantially increase our commercialization costs and expenses, which in turn could delay or prevent us from generating significant revenues from its sale.

There is no assurance that we will be able to successfully integrate Baergic or develop BAER-101 or AJ201.

There can be no assurance that we will have sufficient capital resources to adequately integrate Baergic or develop BAER-101 or AJ201. In addition, as with any of our product candidates, we are subject to many external third party risks including regulatory and manufacturing. We could experience financial or other setbacks if our integration of BAER-101 or AJ201 encounters unanticipated problems, including problems related to execution, integration or underperformance relative to prior expectations. Our management may not be able to successfully integrate any acquired business into our operations or maintain our standards, controls and policies, which could have a material adverse effect on our business, results of operations and financial condition. Consequently, any acquisition we complete may not result in long-term benefits to us or we may not be able to further develop the acquired business in the manner we anticipated. We may need to rely on Fortress to provide administrative and other support, including financial reporting and internal controls, and other transition services to Baergic following our acquisition for a period of time. The failure of the Company to receive such support in a manner that is acceptable to us, could result in a material adverse effect on our business, results of operations and financial condition.

We may not be able to manage our business effectively if we are unable to attract and retain key personnel.

We may not be able to attract or retain qualified management and commercial, scientific and clinical personnel in the future due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses. If we are not able to attract and retain necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy, any of which may have a material adverse effect on our business, financial condition and results of operations.

Our employees, consultants, or third-party partners may engage in misconduct or other improper activities, including those that result in noncompliance with certain regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees, consultants or third-party partners could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee, consultant or third-party misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation, as well as civil and criminal liability. The precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other civil and/or criminal sanctions.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could harm our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. Although we believe that the safety procedures for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties for failure to comply with such laws and regulations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities.

We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

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.

We are a smaller reporting company, and we will remain a smaller reporting company until the fiscal year following the determination that our voting and non-voting common equity held by non-affiliates is more than $250 million measured on the last business day of our second fiscal quarter, or our annual revenues are more than $100 million during the most recently completed fiscal year and our voting and non-voting common equity held by non-affiliates is more than $700 million measured on the last business day of our second fiscal quarter. Smaller reporting companies are able to provide simplified executive compensation disclosure, are exempt from the auditor attestation requirements of the Sarbanes-Oxley Act, and have certain other reduced disclosure obligations, including, among other things, being required to provide only two years of audited financial statements and not being required to provide selected financial data, supplemental financial information or risk factors.

We have elected to take advantage of certain of the reduced reporting obligations. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be reduced or more volatile.

We are a "controlled company" within the meaning of Nasdaq listing standards and, as a result, qualify for, and rely on, exemptions from certain corporate governance requirements. You will not have the same protections afforded to stockholders of companies that are subject to such requirements.

We are a "controlled company" within the meaning of Nasdaq listing standards. Under these rules, a company of which more than 50% of the voting power is held by an individual, a group or another company is a "controlled company" and may elect not to comply with certain corporate governance requirements of Nasdaq, including (i) the requirement that a majority of the Board of Directors consist of independent directors, (ii) the requirement that we have a nominating and corporate governance committee that is composed entirely of independent directors with a written charter addressing the committee's purpose and responsibilities and (iii) the requirement that we have a compensation committee that is composed entirely of independent directors with a written charter addressing the committee's purpose and responsibilities. We have in the past relied on, and intend to continue to rely on, some or all of these exemptions.

Accordingly, you will not have the same protections afforded to stockholders of companies subject to all of the corporate governance requirements of Nasdaq.

Certain of our directors currently serve, and in the past, certain officers and directors have served in similar roles with our parent company, affiliates, related parties and other parties with whom we transact business; ongoing and future relationships and transactions between these parties could result in conflicts of interest.

We sometimes share directors and/or officers with certain of our parent company, affiliates, related parties or other companies with which we transact business, and such arrangements could create conflicts of interest in the future, including with respect to the allocation of corporate opportunities. While we believe that we have put in place policies and procedures to identify such conflicts and that any existing agreements that may give rise to such conflicts and any such policies or procedures were negotiated at arm's length in conformity with fiduciary duties, such conflicts of interest may nonetheless arise. The existence and consequences of such potential conflicts could expose us to lost profits, claims by our investors and creditors, violations of Nasdaq's director and audit committee independence rules and harm to our results of operations.

Risks Pertaining to Our Finances

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 have a limited operating history. We have focused primarily on in-licensing and developing IV Tramadol, with the goal of supporting regulatory approval for this product candidate. We also recently acquired two new product candidates, BAER-101 and AJ201, which we are developing. We have incurred losses since our inception in February 2015.

These losses, among other things, have had and will continue to have an adverse effect on our stockholders' equity and working capital. We expect to continue to incur significant operating losses for the foreseeable future. We also do not anticipate that we will achieve profitability for a period of time after generating material revenues, if ever. If we are unable to generate revenues, we will not become profitable and may be unable to continue operations without continued funding. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the timing or amount of increased expenses or when or if, we will be able to achieve profitability. In addition, the Company cannot be certain that additional funding will be available on acceptable terms, or at all.

Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially if:

- our product candidates or other future product candidates are approved for commercial sale, due to the necessity in establishing adequate commercial infrastructure to launch such candidate or candidates without substantial delays, including hiring, sales and marketing personnel, and contracting with third parties for warehousing, distribution, cash collection and related commercial activities;
- we are required by the FDA, or foreign regulatory authorities, to perform studies in addition to those currently expected;
- there are any delays in completing our clinical trials or the development of any of our product candidates;
- we execute other collaborative, licensing or similar arrangements and the timing of payments we may make or receive under these arrangements;
- there are variations in the level of expenses related to our future development programs;
- there are any product liability or intellectual property infringement lawsuits in which we may become involved; and
- there are any regulatory developments affecting our product candidates or the product candidates of our competitors.

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated any revenue from our development stage product, and we do not know when, or if, we will generate any revenue. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- obtain regulatory approval for our product candidates or any other product candidates that we may license or acquire;
- manufacture commercial quantities of our product candidates or other product candidates, if approved, at acceptable cost levels; and
- develop a commercial organization and the supporting infrastructure required to successfully market and sell our product candidates, if approved.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress our value and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in our value could also cause you to lose all or part of your investment.

Our short operating history makes it difficult to evaluate our business and prospects.

We were incorporated on February 9, 2015, and until our acquisition of Baergic had only been conducting operations with respect to IV Tramadol since February 17, 2015. We have not yet demonstrated an ability to successfully obtain regulatory approvals, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, any predictions about our future performance may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products.

In addition, as a young business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will need to expand our capabilities to support commercial activities and the recent acquisitions of AJ201 and BAER-101. We may not be successful in adding such capabilities.

We expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any past quarterly period as an indication of future operating performance.

There is substantial doubt about our ability to continue as a going concern, which may hinder our ability to obtain future financing.

Our audited consolidated financial statements as of December 31, 2022 have been prepared under the assumption that we will continue as a going concern for the next twelve months. As of December 31, 2022, we had cash and cash equivalents of $6.7 million and an accumulated deficit of $80.6 million. We do not believe that our cash and cash equivalents are sufficient for the next twelve months. As a result of our financial condition and other factors described herein, there is substantial doubt about our ability to continue as a going concern. Our ability to continue as a going concern will depend on our ability to obtain additional funding, as to which no assurances can be given. We continue to analyze various alternatives, including potentially obtaining lines of credit, debt or equity financings or other arrangements. Our future success depends on our ability to raise capital and/or implement the various strategic alternatives discussed above. We cannot be certain that these initiatives or raising additional capital, whether through selling additional debt or equity securities or obtaining a line of credit or other loan, will be available to us or, if available, will be on terms acceptable to us. If we issue additional securities after the closing of this offering to raise funds, these securities may have rights, preferences, or privileges senior to those of our common stock, and our current shareholders may experience dilution. If we are unable to obtain funds when needed or on acceptable terms, we may be required to curtail our current development programs, cut operating costs, forego future development and other opportunities or even terminate our operations.

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.

We have not generated any product related revenues to date. To obtain revenues from sales of our product candidates, we must succeed, either alone or with third parties, in developing, obtaining regulatory approval for, manufacturing and marketing products with commercial potential. We may never succeed in these activities, and we may not generate sufficient revenues to continue our business operations or achieve 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.

Our operations have consumed substantial amounts of cash since inception. We expect to significantly increase our spending to advance the clinical development and potential regulatory approval of our product candidates and launch and commercialize any additional product candidates for which we receive regulatory approval, including building our own commercial organizations to address certain markets. Even after the completion of future offerings, we may require additional capital for the further development and potential commercialization of our product candidates, as well as to fund our other operating expenses and capital expenditures, and cannot provide any assurance that we will be able to raise funds to complete the development of our products.

We cannot be certain that additional funding will be available on acceptable terms, or at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates. We may also seek collaborators for product candidates at an earlier stage than otherwise would be desirable or on terms that are less favorable than might otherwise be available. Any of these events could significantly harm our business, financial condition and prospects.

Our future funding requirements will depend on many factors, including, but not limited to:

- the potential for delays in our efforts to seek regulatory approval for our product candidates, and any costs associated with such delays;
- the costs of establishing a commercial organization to sell, market and distribute our product candidates;
- the rate of progress and costs of our efforts to prepare for the submission of an NDA for any product candidates that we may in-license or acquire in the future, and the potential that we may need to conduct additional clinical trials to support applications for regulatory approval;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights associated with our product candidates, including any such costs we may be required to expend if our licensors are unwilling or unable to do so;
- the cost and timing of securing sufficient supplies of our product candidates from our contract manufacturers in preparation for commercialization;
- the effect of competing technological and market developments;
- the terms and timing of any collaborative, licensing, co-promotion or other arrangements that we may establish;
- if one or more of our product candidates are approved, the potential that we may be required to file a lawsuit to defend our patent rights or regulatory exclusivities from challenges by companies seeking to market generic versions of one or more of our product candidates; and
- the success of the commercialization of one or more of our product candidates.

In order to carry out our business plan and implement our strategy, we may need to obtain additional financing and may choose to raise additional funds through strategic collaborations, licensing arrangements, public or private equity or debt financing, bank lines of credit, asset sales, government grants, or other arrangements. We cannot be sure that any additional funding, if needed, will be available on terms favorable to us or at all. Furthermore, any additional equity or equity-related financing may be dilutive to our stockholders, and debt or equity financing, if available, may subject us to restrictive covenants and significant interest costs. If we obtain funding through a strategic collaboration or licensing arrangement, we may be required to relinquish our rights to our product candidates or marketing territories.

Our inability to raise capital when needed would harm our business, financial condition and results of operations, and could cause our stock value to decline or require that we wind down our operations altogether.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish proprietary rights.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, grants and license and development agreements in connection with any collaborations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market any potential product candidates that we would otherwise prefer to develop and market ourselves.

We have in the past failed to satisfy applicable listing standards of the Nasdaq Capital Market and could fail to satisfy those requirements again in the future, which could result in our common stock being delisted from the Nasdaq Capital Market.

Currently our common stock trades on the Nasdaq Capital Market. During 2021 and 2022, we received notification from the Listing Qualifications Department of the Nasdaq Stock Market ("Nasdaq") informing us of certain listing deficiencies related to the minimum required market value of listed securities, minimum stockholders' equity and minimum bid price listing requirements, which led to the issuance of delisting notices. Although we have since cured these deficiencies and our common stock continues to trade on the Nasdaq Capital Market, it is possible that we could fall out of compliance again in the future. If we fail to maintain compliance with any Nasdaq listing requirements, our common stock could be delisted from the Nasdaq Capital Market. This could severely limit the liquidity of our common stock and your ability to sell our securities on the secondary market. Delisting from the Nasdaq could adversely affect our ability to raise additional financing through the public or private sale of equity securities, would significantly affect the ability of investors to trade our securities and would negatively affect the value and liquidity of our common stock. Delisting could also have other negative results, including the potential loss of confidence by employees, the loss of institutional investor interest and fewer business development opportunities. If our common stock is delisted by the Nasdaq the price of our common stock may decline and our common stock may be eligible to trade on the OTC Bulletin Board, another over-the-counter quotation system, or on the pink sheets where an investor may find it more difficult to dispose of their common stock or obtain accurate quotations as to the market value of our common stock. Further, if we are delisted, we would incur additional costs under requirements of state "blue sky" laws in connection with any sales of our securities. These requirements could severely limit the market liquidity of our common stock and the ability of our stockholders to sell our common stock in the secondary market.

Risks Pertaining to Reliance on Third Parties

If any of our product candidates are approved and our contract manufacturer fails 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 that product candidate, lose potential revenues or be unable to meet market demand.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls, and the use of specialized processing equipment. We have entered into a development and supply agreement for the completion of pre-commercialization manufacturing development activities and the manufacture of commercial supplies of IV Tramadol. Any termination or disruption of this relationship may materially harm our business and financial condition, and impact any commercialization efforts for this product candidate.

In order to meet anticipated demand for IV Tramadol, if this product candidate is approved, we currently have one manufacturer to provide us clinical and commercial supply of IV Tramadol in accordance with the CGMP requirements. We also may plan to qualify a backup manufacturer, in order to ensure an alternative source and to mitigate any potential supply issues. We have sufficient drug substance for BAER-101 on hand to execute our planned near-term studies, and are in process of identifying future manufacturers. AnnJi, from whom we license the intellectual property underlying AJ201, has committed to provide us with limited supplies of this product candidate, but we will need to secure longer-term manufacturing sources to complete development and commercialization of this product. Failure to secure such sources could have a material adverse effect on our ability to pursue these product candidates.

All of our contract manufacturers must comply with strictly enforced federal, state and, where applicable, foreign regulations, including CGMP requirements enforced by the FDA through its inspectional authority over facilities under the FDCA, as well requirements for controlled substance handling and security requirements enforced by DEA, and while we exercise oversight of our suppliers, we have limited direct control over their compliance with these regulations, as reflected in day-to-day operations. Any failure to comply with applicable regulations may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval, and would limit the availability of our product. Any quality or compliance issue, manufacturing defect or error discovered after products have been produced and distributed could result in even more significant consequences, including costly recall procedures, re-stocking costs, damage to our reputation and potential for product liability claims.

If the commercial manufacturers upon whom we rely to manufacture our product candidates we may in-license, fail to deliver sufficient commercial quantities on a timely basis at commercially reasonable prices, we would likely be unable to meet demand for our products and we would lose potential revenues, which could have a material adverse effect on our business, financial condition and results of operations.

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 have relied on third party contract research organizations and clinical research organizations to conduct some of our preclinical studies and all of our clinical trials for IV Tramadol and may do so for BAER-101, AJ201 and any other future product candidates. We may continue to rely on third parties, such as contract research organizations, clinical research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct preclinical studies and clinical trials. The agreements with these third parties might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that could delay our product development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our legal and regulatory product development responsibilities. For example, we will remain responsible for ensuring that each of our preclinical studies and clinical trials are conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our preclinical studies are conducted in accordance with good laboratory practice, or "GLP", as appropriate. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, or "GCPs", for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of our clinical research organizations fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable or unacceptable, and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted using products manufactured and produced in accordance with CGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

The third parties with whom we have contracted to help perform our preclinical studies or clinical trials may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, potentially successfully commercialize our product candidates.

If any of our relationships with these third-party contract research organizations or clinical research organizations terminates, we may not be able to enter into arrangements with alternative contract research organizations or clinical research organizations or to do so on commercially reasonable terms. Switching or adding additional contract research organizations or clinical research organizations involves additional cost and requires extensive training and management time and focus. In addition, there is a natural transition period when a new contract research organization or clinical research organization commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our contract research organizations or clinical research organizations, there can be no assurance that we will not encounter challenges or delays in the future.

We contract with third parties for the manufacture of our product candidates for preclinical and clinical testing and expect to continue to do so for potential commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our potential product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not own any manufacturing facilities or employ any manufacturing personnel. We rely, and expect to continue to rely, on third-party manufacturers to manufacture our product candidates for preclinical and clinical testing, as well as for commercial manufacture, once any of our product candidates receives marketing approval. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or potential commercialization efforts.

We may be unable to establish any agreements with such third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third party manufacturers, reliance on third-party manufacturers entails additional risks, including, but not necessarily limited to:

- reliance on the third party for regulatory compliance and quality assurance;
- raw material or active ingredient shortages from suppliers the third party has qualified for our product;
- the possible breach of the manufacturing agreement by the third party;
- manufacturing delays if our third-party manufacturers give greater priority to the supply of other products over our product candidates or otherwise do not satisfactorily perform according to the terms of the agreement between us;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

The facilities used by our contract manufacturers to manufacture our product candidates is subject to registration requirements, and inspection by the FDA. A pre-approval inspection may be conducted after the submission of an application to the FDA. Although we will have oversight over our suppliers and manufacturers, we do not directly control the manufacturing operations and processes at these facilities, and therefore rely on, our contract manufacturers to ensure full compliance with CGMP regulations with respect to the day-to-day operations related to the manufacture of our product candidates. Third-party manufacturers may, following an inspection, be subject to a Form FDA-483 or similar inspectional findings, or a Warning Letter, or may not otherwise be able to comply with the CGMP regulations or similar regulatory requirements outside the United States. The failure of our third-party manufacturers to comply with applicable regulations directly impacts our compliance and could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. There may be a limited number of manufacturers that both operate under CGMP regulations and are capable of manufacturing for us. Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current contract manufacturers cannot perform as agreed, we may be required to replace such manufacturers. We may incur added costs and delays in identifying and qualifying any replacement manufacturers.

The DEA restricts the importation of a controlled substance finished drug product when the same substance is commercially available in the United States, which could reduce the number of potential alternative manufacturers for IV Tramadol.

Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to potentially commercialize any products that receive marketing approval on a timely and competitive basis.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or potential commercialization of our products, producing additional losses and depriving us of potential product revenue.

We rely on clinical data and results obtained by third parties that could ultimately prove to be inaccurate or unreliable.

As part of our strategy to mitigate development risk, we seek to develop product candidates with a validated mechanism of action, and we utilize biomarkers to assess potential clinical efficacy early in the development process. This strategy necessarily relies upon clinical data and other results obtained by third parties that may ultimately prove to be inaccurate or unreliable. Further, such clinical data and results may be based on products or product candidates that are significantly different from our product candidates or future product candidates. If the third-party data and results we rely upon prove to be inaccurate, unreliable or not applicable to our product candidates or future product candidate, we could make inaccurate assumptions and conclusions about our product candidates and our research and development efforts could be compromised and called into question during the review or any marketing applications we submit.

Risks Pertaining to Regulatory Approval Process

We may not receive regulatory approval for IV Tramadol, or our approval may be significantly delayed due to scientific or regulatory reasons.

While we acquired BAER-101 in connection with our acquisition of Baergic, we continue to pursue regulatory approval for IV Tramadol. However, in light of recently disclosed developments, there is doubt about our ability to obtain regulatory approval for IV Tramadol. In December 2019, we submitted an NDA for IV Tramadol and received the First CRL from the FDA in October 2020. In February 2021, we resubmitted the NDA for IV Tramadol. The FDA assigned a PDUFA goal date of April 12, 2021 for the resubmitted NDA for IV Tramadol. On June 14, 2021, we announced that we had received 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 an FDRR with the Office of New Drugs of the FDA. On October 21, 2021, we received a written response from the Office of New Drugs 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 Office of New Drugs in response to the FDRR.

Following the receipt of the Appeal Denied Letter, we submitted a Type A Meeting Request and related briefing document to the FDA on June 17, 2022. The meeting was granted by the Division of Anesthesia, Analgesia, and Addiction Products ("DAAAP") on June 27, 2022, and scheduled for August 9, 2022. We submitted a briefing document presenting a study design that we believe has the potential to address the concerns around the safety risk of IV Tramadol in combination with other opioid analgesics for the management of moderate-to-moderately-severe pain in adults in a medically supervised healthcare setting that was discussed in detail at the previously disclosed Advisory Committee meeting on February 15, 2022 and in the Appeal Denied letter received on March 18, 2022.

The meeting on August 9, 2022 was a collaborative discussion on the study design and potential path forward. At the meeting, we presented a study design for a single safety clinical trial that we believe could address the concerns regarding risks related to opioid stacking. The FDA stated that the proposed study design appears reasonable and agreed on various study design aspects with the expectation that additional feedback would be provided to us upon review of a more detailed study protocol. We intend to incorporate the FDA's suggestions from the meeting minutes and submit a detailed study protocol that could form the basis for the submission of a complete response to the second Complete Response Letter for IV Tramadol.

Following the Type A Meeting, we submitted a subsequent request to the FDA and were granted a Type C Meeting 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. If the FDA does not approve, or significantly delays the approval of, IV Tramadol, it could cause a material adverse effect on our business, financial condition and results of operations.

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 product candidates and any other product candidates we may license or acquire will also be subject to ongoing regulatory and compliance requirements, including regular inspections by the FDA and other regulatory authorities. These requirements relate to, among others, labeling, packaging, storage, advertising, promotion, record-keeping and submission of safety and other post-market

information and reports, registration and listing requirements, ongoing CGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping of the drug.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance programs to monitor the safety or efficacy of the product. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and off-label information and if we do not market our products for only their approved indications and on-label information, we may be subject to enforcement action for off-label marketing as well as false claims liability. Violations of the FDCA relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our product, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such product, operations, manufacturers or manufacturing processes;
- restrictions or new requirements related to the promotion, labeling or marketing of a product;
- restrictions on product distribution or use, including import and export restrictions;
- requirements to conduct post-marketing studies or clinical trials;
- Form FDA-483 findings, or warning letters;
- recall of the product, or withdrawal of the product from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- fines, restitution or disgorgement of profits;
- suspension or withdrawal of marketing or regulatory approvals;
- suspension of any ongoing clinical trials;
- refusal to permit the import or export of our product;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies, as well as policies of the DEA, who has jurisdiction over controlled substances and opioids, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidate. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained.

We will need to obtain FDA approval of any proposed product brand names, and any failure or delay associated with such approval may adversely impact our business.

A pharmaceutical product candidate cannot be marketed in the United States or many other countries until we have completed a rigorous and extensive regulatory review processes, including obtaining the approval of a brand name. Any brand names we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the U.S. Patent and Trademark Office, or "USPTO". The FDA typically conducts a review of proposed product brand names, including an evaluation of potential for confusion with other product names. The FDA may also object to a product brand name if it believes the name inappropriately implies medical claims. If the FDA objects to any of our proposed product brand name, we may be

required to adopt an alternative brand name for our product candidate. If we adopt an alternative brand name, we would lose the benefit of our existing trademark applications for such product candidate and may be required to expend significant additional resources in an effort to identify a suitable product brand name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. We may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our ability to potentially commercialize our product candidate.

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.

Healthcare providers, physicians and third-party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors, distributors, retailers, marketers and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations, including, without limitation, the federal Anti-Kickback Statute, the federal False Claims Act, and similar state or foreign laws which may constrain the business or financial arrangements and relationships through which we sell, market and distribute any product candidates for which we obtain marketing approval. In addition, we may be subject to transparency laws and patient privacy regulation by U.S. federal and state governments and by governments in foreign jurisdictions in which we conduct our business. The applicable federal, state and foreign healthcare laws and regulations that may affect our ability to operate include, but are not necessarily limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs, such as Medicare and Medicaid;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act, which impose criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, including the Medicare and Medicaid programs, claims for payment that are false or fraudulent, making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government, or the knowing retention of an overpayment from government health care programs; the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose obligations on covered healthcare providers, health plans, and healthcare clearinghouses, as well as their business associates that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

- the federal Open Payments program, which requires manufacturers of certain drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or "CMS", information related to "payments or other transfers of value" made to physicians, which is defined to include doctors, dentists, optometrists, podiatrists and chiropractors, and certain teaching hospitals and applicable manufacturers to report annually to CMS ownership and investment interests held by the physicians and their immediate family members; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers; state and foreign laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government or otherwise restrict payments that may be made to healthcare providers; state and foreign laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations may involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, including, without limitation, damages, fines, imprisonment, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations, which could have a material adverse effect on our business. If any of the physicians or other healthcare providers or entities with whom we expect to do business, including our collaborators, is found not to be in compliance with applicable laws, it may be subject to criminal, civil or administrative sanctions, including exclusions from participation in government healthcare programs, which could also materially affect our business, financial condition and results of operations.

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.

Any regulatory approval is limited to the specific labeled indication(s) for which a product is deemed to be safe and effective by the FDA. In addition to the FDA approval required for new formulations, any new indication for an approved product also requires FDA approval. If we are not able to obtain FDA approval for any desired future indications for our product, our ability to effectively potentially market and sell our product may be reduced and our business may be adversely affected.

While physicians may choose to prescribe drugs for uses that are not described in the product's approved labeled indication, or for uses that differ from those tested in clinical studies, and thus the basis for approval by the regulatory authorities, our ability to promote the products is limited to those indications that are specifically approved by the FDA. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the United States generally do not regulate the practice of medicine by physicians with respect to their choice of treatments. Regulatory authorities do, however, restrict communications by pharmaceutical companies in terms of their ability to promote off-label uses or disseminate off-label information. If our promotional activities fail to comply with these requirements, we may be subject to regulatory, compliance, or enforcement action by, these authorities. In addition, our failure to follow FDA requirements relating to promotion and advertising may result in a Warning Letter, cause the FDA to suspend or withdraw an approved product from the market, require a recall, require the issuance of corrective advertising, institute fines, or could result in disgorgement of money, operating restrictions, injunctions or civil or criminal prosecution by the government, any of which could harm our reputation and business.

If the DEA 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.

In July 2014, the DEA classified Tramadol as a Schedule IV controlled substance. In comparison, other opioids, which have a high potential for abuse, are classified as Schedule I and II controlled substances. If approved, IV Tramadol will be the only intravenous Schedule IV opioid on the market. However, in the current environment where the opioid epidemic is a recognized problem in the United States, there is a possibility that the DEA could reschedule Tramadol to a more restrictive classification (Schedule I, II or III). Such a rescheduling, or other similar action by DEA, would severely impair IV Tramadol's current competitive advantage over traditional opioids and may affect our ability to potentially market IV Tramadol as a safe alternative pain management product.

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.

In the United States and certain foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system that could prevent or delay marketing approval of our product candidate, restrict or regulate post-approval activities, and affect our ability to profitably sell any product candidates for which we obtain marketing approval. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (the "PPACA" or collectively, the "ACA"), substantially regulates the way healthcare is financed by both governmental and private insurers in the United States. Among other things, the ACA increased the minimum level of Medicaid rebates payable by manufacturers of brand name drugs from 15.1% to 23.1%; required collection of rebates for drugs paid by Medicaid managed care organizations; imposed a non-deductible annual fee on pharmaceutical manufacturers or importers who sell certain "branded prescription drugs" to specified federal government programs; implemented a new methodology under which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected; expanded the eligibility criteria for

Medicaid programs; created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare and Medicaid Innovation ("CMMI") at the CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment, there have been executive, judicial and Congressional challenges to certain aspects of the ACA, and we expect there will be additional challenges and amendments to the ACA in the future. On January 20, 2017, President Donald Trump signed an executive order stating that the administration intended to seek prompt repeal of the Affordable Care Act, and, pending repeal, directed the U.S. Department of Health and Human Services and other executive departments and agencies to take all steps necessary to limit any fiscal or regulatory burdens of the Affordable Care Act. On January 28, 2021, President Joe Biden signed the Executive Order on Strengthening Medicaid and stated his administration's intentions to reverse the actions of his predecessor and strengthen the Affordable Care Act. As part of this Executive Order, the Department of Health and Human Services, United States Treasury, and the Department of Labor are to review all existing regulations, orders, guidance documents, policies, and agency actions to consider if they are consistent with ensuring both coverage under the Affordable Care Act and if they make high-quality healthcare affordable and accessible to Americans. On March 11, 2021, President Biden signed into law the American Rescue Plan Act of 2021 to further strengthen Medicaid and the ACA and on April 5, 2022, President Biden signed the Executive Order on Continuing to Strengthen Americans' Access to Affordable, Quality Health Coverage in which he celebrated the significant progress across the U.S. in making healthcare more affordable and accessible. In this Executive Order, President Biden directed agencies "with responsibilities related to Americans' access to health coverage" to "review agency actions to identify ways to continue to expand the availability of affordable health coverage." The continued expansion of the government's role in the U.S. healthcare industry may further lower rates of reimbursement for pharmaceutical products. While we are unable to predict the likelihood of changes to the Affordable Care Act or other healthcare laws which may negatively impact our profitability, we continue to closely monitor all changes.

President Biden intends to take action against drug prices which are considered "high." Drug pricing continues to be a subject of debate at the executive and legislative levels of U.S. government. The American Rescue Plan Act of 2021 signed into law by President Joseph R. Biden Jr. on March 14, 2021 includes a provision that will eliminate the statutory cap on rebates drug manufacturers pay to Medicaid beginning in January 2024. With the elimination of the rebate cap, manufacturers may be required to compensate states in an amount greater than what the state Medicaid programs pay for the drug. Additionally, the Inflation Reduction Act of 2022 contains substantial drug pricing reforms, including the establishment of a drug price negotiation program within the U.S. Department of Health and Human Services that would require manufacturers to charge a negotiated "maximum fair price" for certain selected drugs or pay an excise tax for noncompliance, the establishment of rebate payment requirements on manufacturers of certain drugs payable under Medicare Parts B and D to penalize price increases that outpace inflation, and requires manufacturers to provide discounts on Part D drugs. Substantial penalties can be assessed for noncompliance with the drug pricing provisions in the Inflation Reduction Act of 2022. The Inflation Reduction Act of 2022 could have the effect of reducing the prices we can charge and reimbursement we receive for our products, if approved, thereby reducing our profitability, and could have a material adverse effect on our financial condition, results of operations and growth prospects. The effect of Inflation Reduction Act of 2022 on our business and the pharmaceutical industry in general is not yet known.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that additional federal, state and foreign healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, once approved, or additional pricing pressures.

These and other healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any current product or future product candidate. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products. Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of any current or future product candidates, if any, may be. In addition, increased Congressional scrutiny of the

FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

Public concern regarding the safety of opioid drug products such as IV Tramadol could delay or limit our ability to obtain regulatory approval for this product, 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.

In light of widely publicized events concerning the safety risk of certain drug products, the FDA, members of Congress, the Government Accountability Office, medical professionals and the general public have raised concerns about potential controlled substance drug safety issues. These events have resulted in the withdrawal of drug products, revisions to drug labeling that further limit use of the drug products and the establishment of risk management programs. Under the Food and Drug Administration Amendments Act of 2007, or "FDAAA", the FDA has authority to, among other things, require post-approval studies and clinical trials, mandate changes to drug labeling to reflect new safety information and require risk evaluation and mitigation strategies for certain drugs, including certain currently approved drugs. The FDAAA also expanded the federal government's clinical trial registry and results databank, resulting in significantly increased government oversight of clinical trials. Under the FDAAA, companies that violate these and other provisions of the law are subject to substantial civil monetary penalties, among other regulatory, civil and criminal penalties. The increased attention to drug safety issues may result in a more cautious approach by the FDA in its review of data from our clinical trials. Data from clinical trials may receive greater scrutiny, particularly with respect to safety, which may make the FDA or other regulatory authorities more likely to require additional preclinical studies or clinical trials. If the FDA requires us to conduct additional preclinical studies or clinical trials prior to approving IV Tramadol, our ability to obtain approval of this product candidate will be delayed. If the FDA requires us to provide additional clinical or preclinical data following the approval of IV Tramadol, the indications for which this product candidate is approved may be limited or there may be specific warnings or limitations on production dosing, and our efforts to commercialize IV Tramadol may be otherwise adversely impacted.

Rising public, medical, Congressional, and agency concern around the prescription of controlled substance drug products to patients and a growing movement to reduce the use of opioid drug products, to develop abuse-deterrent products, and to prevent dependence also could negatively impact our ability to commercialize and generate revenue from IV Tramadol if it is approved for marketing in the United States. Congress has enacted several laws intended to address opioid use disorder, including the Comprehensive Addiction and Recovery Act (CARA) in 2016, the 21st Century Cures Act (Cures Act) in 2016, and the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (the SUPPORT Act) in 2018. These laws primarily focus on funding for treatment, research, and education, but also include provisions intended to encourage reduction in opioid use, such as funding for research on non-opioid pain treatments. Other legislative and administrative measures at the state and federal level include, or may include in the future, restrictions and limitations on opioid prescribing, limitations on opioid doses dispensed per episode of care, labeling requirements specific to opioids, limitations on FDA approval of opioids, assessment of fees against opioid manufacturers, or reimbursement disincentives specific to opioids.

We expect intense competition for our product candidates, and new products may emerge that provide different or better therapeutic alternatives for our targeted indications.

The biotechnology and pharmaceutical industries are subject to rapid and intense technological change. We face, and will continue to face, competition in the development and marketing of our product candidates from academic institutions, government agencies, research institutions and biotechnology and pharmaceutical companies. There can be no assurance that developments by others will not render our product candidates obsolete or noncompetitive. Furthermore, new developments, including the development of other drug technologies and methods of preventing the incidence of disease, occur in the pharmaceutical industry at a rapid pace. These developments may render on or more of our product candidates obsolete or noncompetitive.

IV Tramadol will compete with well-established products with similar indications. Competing products available for the management of pain include other approved opioid agonists such as morphine, hydromorphone, fentanyl and oliceridine (approved in 2020 by the FDA). Non-opioid products include Ofirmev (IV acetaminophen) and IV formulations of NSAIDs such as Dyloject (diclofenac), Toradol (ketorolac), Anjeso (meloxicam) and Caldolor (ibuprofen). In addition, we also expect to compete with agents such as Exparel, a liposome injection of bupivacaine indicated for administration into the surgical site to produce postsurgical analgesia. In addition to approved products, there are a number of product candidates in development for the management of acute pain. The late-stage pain development pipeline is replete with reformulations and fixed-dose combination products of already available therapies. Among specific drug classes, opioid analgesics and NSAIDs represent the greatest number of agents in development. Most investigational opioids that have reached the later stages of clinical development are new formulations of already marketed opioids.

Likewise, investigational NSAIDs — mostly lower dose injectable reformulations of already approved compounds — are another significant area of late-stage drug development in the postoperative pain space.

BAER-101 competitors in the GABA-A space are in the clinic and include Cerevel Therapeutics (darigabat), RespireRx Pharmaceuticals (KRM-II-81), Saniona AB (SAN711), and Engrail Therapeutics (ENX101).

Although there are no approved therapies to treat SBMA, AJ201 competitors include Nido Biosciences (NIDO-361) and pre-clinical programs from academic institutions. In Japan, Leuprorelin is approved for SBMA, but has not been developed for the indication in the United States.

The commercial opportunity for our products could be significantly harmed if competitors are able to develop alternative formulations outside the scope of our in-licensed patents. Compared to us, many of our potential competitors have substantially greater:

- capital resources;
- development resources, including personnel and technology;
- clinical trial experience;
- regulatory experience;
- expertise in prosecution of intellectual property rights; and
- manufacturing, distribution and sales and marketing experience.

As a result of these factors, our competitors may obtain regulatory approval of their products more rapidly than we are able to or may obtain patent protection or other intellectual property rights that limit our ability to develop or potentially commercialize our product candidates. Our competitors may also develop drugs that are more effective, safe, useful and less costly than ours and may be more successful than us in manufacturing and marketing their products.

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.

Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower-cost drugs and may be incorporated into existing payments for other services. In both domestic and foreign markets, our sales of any future products will depend in part upon the availability of coverage and reimbursement from third party payors. Such third-party payors include government health programs such as Medicare and Medicaid, managed care providers, private health insurers and other organizations. In particular, many U.S. hospitals receive a fixed reimbursement amount per procedure for certain surgeries and other treatment therapies they perform. Because this amount may not be based on the actual expenses the hospital incurs, hospitals may choose to use therapies which are less expensive when compared to our product candidates or future product candidates. Accordingly, our product candidates or any other product candidates that we may in-license or acquire, if approved, will face competition from other therapies and drugs for these limited hospital financial resources. We may need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to the satisfaction of hospitals, other target customers and their third-party payors. Such studies might require us to commit a significant amount of management time and financial and other resources. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by implementation of recently promulgated regulations that permit importation of drugs from countries where they may be sold at lower prices than in the United States. Our future product might not ultimately be considered cost-effective. Adequate third-party coverage and reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

If none of our product candidates achieves broad market acceptance, the potential revenues that we generate from sales will be limited.

The commercial success of our product candidates or any or all of them, if approved, will depend upon its acceptance by the medical community, the ability to ensure that the drug is included in hospital formularies, and coverage and reimbursement for the drug by third

party payors, including government payors. The degree of market acceptance of our product candidates or any other product candidate we may license or acquire would depend on a number of factors, including, but not necessarily limited to:

- the efficacy and safety as demonstrated in clinical trials;
- the safety and use of our product candidates in its intended patient population;
- the timing of market introduction of our product candidates as well as competitive products;
- the clinical indications for which the drug is approved;
- acceptance by physicians, major operators of hospitals and clinics and patients of the drug as a safe and effective treatment;
- the safety of our product candidates seen in a broader patient group (i.e., real world use);
- the availability, cost and potential advantages of alternative treatments, including less expensive generic drugs;
- the availability of adequate reimbursement and pricing by third party payors and government authorities;
- the relative convenience and ease of administration of our product candidates for clinical practices;
- the product labeling or product insert required by the FDA or regulatory authority in other countries, including any contradictions, warnings, drug interactions, or other precautions;
- the approval, availability, market acceptance and reimbursement for a companion diagnostic, if any;
- the prevalence and severity of adverse side effects;
- the effectiveness of our sales and marketing efforts;
- changes in the standard of care for the targeted indications for our product candidates or future product candidates, which could reduce the marketing impact of any superiority claims that we could make following FDA approval; and
- potential advantages over, and availability of, alternative treatments.

If any product candidate that we develop does not provide a treatment regimen that is as beneficial as, or is not perceived as being as beneficial as, the current standard of care or otherwise does not provide patient benefit, that product candidate, if approved for commercial sale by the FDA or other regulatory authorities, likely will not achieve market acceptance. Our ability to effectively promote and potentially sell our product candidates and any other product candidates we may license or acquire in the hospital marketplace will also depend on pricing and cost effectiveness, including our ability to produce a product at a competitive price and achieve acceptance of the product onto hospital formularies, as well as our ability to obtain sufficient third-party coverage or reimbursement. Since many hospitals are members of group purchasing organizations, which leverage the purchasing power of a group of entities to obtain discounts based on the collective buying power of the group, our ability to potentially attract customers in the hospital marketplace will also depend on our ability to effectively potentially promote our product candidates to group purchasing organizations. We will also need to demonstrate acceptable evidence of safety and efficacy, as well as relative convenience and ease of administration. Market acceptance could be further limited depending on the prevalence and severity of any expected or unexpected adverse side effects associated with our product candidates. If any of our product candidates is approved but does not achieve an adequate level of acceptance by physicians, health care payors and patients, we may not potentially generate sufficient revenue from this product, and we may not become or remain profitable. In addition, our efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful.

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 currently do not have a marketing or sales organization for the marketing and sales of pharmaceutical products since we currently have no drug products for sale. In order to potentially commercialize any product candidate that receives marketing approval, we would need to build out marketing, sales, managerial and other non-technical capabilities or enter into agreements with third party contract organizations to perform these services, and we may not be successful in doing so. In the event of successful development and regulatory approval of our product candidates or another product candidate, we might have to build a targeted specialist sales force to market or co-promote the product. There are risks involved with establishing our own sales and marketing capabilities. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our potential efforts to successfully commercialize our future product, if any, using our own sales and marketing capabilities include, but are not necessarily limited to:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future products;
- the lack of complementary or other products to be offered by sales personnel, which may put us at a competitive disadvantage from the perspective of sales efficiency relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

As an alternative to establishing our own sales force, we may choose to partner with third parties that have well-established direct sales forces to sell, market and distribute our products. There are risks involved with partnering with third party sales forces, including ensuring adequate training on the product, regulatory, and compliance requirements associated with promotion of the product.

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.

The use of our product candidates and any other product candidates we may license or acquire in clinical trials and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Product liability claims might be brought against us by consumers, health care providers or others using, administering or selling our products. If we cannot successfully defend ourselves against these claims, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- withdrawal of clinical trial participants;
- termination of clinical trial sites or entire trial programs;
- decreased demand for any product candidates or products that we may develop;
- initiation of investigations by regulators;
- impairment of our business reputation;
- costs of related litigation;
- substantial monetary awards to patients or other claimants;

- loss of revenues;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize our product candidates or future product candidates.

We have limited product liability insurance coverage for our clinical trials. However, our insurance coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. When needed, we intend to potentially expand our insurance coverage to include the sale of commercial products if we obtain marketing approval for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business, financial condition and results of operations.

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.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection in the United States with respect to our product candidates or any other product candidates that we may license or acquire and the methods we use to manufacture them, as well as successfully defending these patents and trade secrets against third party challenges. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidate. We will only be able to protect our technologies from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. If our licensors or we fail to obtain or maintain patent protection or trade secret protection for our product candidates or any other product candidate we may license or acquire, third parties could use our proprietary information, which could impair our ability to compete in the market and adversely affect our ability to generate revenues and achieve profitability. Moreover, should we enter into other collaborations we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance and enforcement of our patents. Therefore, these patents and applications may not be prosecuted and enforced in a manner consistent with the best interests of our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. In addition, no consistent policy regarding the breadth of claims allowed in pharmaceutical or biotechnology patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after a first filing, or in some cases at all. Therefore, we cannot know with certainty whether we or our licensors were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. In the event that a third party has also filed a U.S. patent application relating to our product candidates or a similar invention, we may have to participate in interference proceedings declared by the USPTO to determine priority of invention in the United States. The costs of these proceedings could be substantial and it is possible that our efforts would be unsuccessful, resulting in a material adverse effect on our U.S. patent position. As a result, the issuance, scope, validity, enforceability and commercial value of our or any of our licensors' patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or products, in whole or in part, or which effectively prevent others from commercializing competitive technologies and products. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. For example, the federal courts of the United States have taken an increasingly dim view of the patent eligibility of certain subject matter, such as naturally occurring nucleic acid sequences, amino acid sequences and certain

methods of utilizing same, which include their detection in a biological sample and diagnostic conclusions arising from their detection. Such subject matter, which had long been a staple of the biotechnology and biopharmaceutical industry to protect their discoveries, is now considered, with few exceptions, ineligible in the first place for protection under the patent laws of the United States. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents (if any) or in those licensed from third parties.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and affect the validity, enforceability, scope or defense of our issued patents. The Leahy-Smith America Invents Act, or the Leahy-Smith Act, includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The USPTO issues and administers regulations and procedures to govern administration of the Leahy-Smith Act, including the first-to-file provisions. The Leahy-Smith Act could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material, adverse effect on our business and financial condition.

Moreover, we may be subject to a third-party pre-issuance submission of prior art to the USPTO, or become involved in opposition, derivation, reexamination, inter parties review, post-grant review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, Patent Trial and Appeal Board ("PTAB") trial, proceeding or litigation could reduce the scope of, render unenforceable, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent does not foreclose challenges to its inventorship, scope, validity or enforceability. Therefore, our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

The patent rights that we have in-licensed covering the infusion time and pharmacokinetics, or "PK", profile for IV Tramadol are limited to a specific IV formulation of centrally acting synthetic opioid analgesic, and our market opportunity for this product candidate may be limited by the lack of patent protection for the active ingredient itself and other formulations that may be developed by competitors.

The active ingredients in IV Tramadol have been generic in the United States for a number of years. While we believe that the patent estate covering IV Tramadol (including but not limited to U.S. Patent Nos. 8,895,622; 9,561,195, 9,566,253 9,962,343, 10,406,122, 9,693,949, 9,968,551, 9,980,900, 10,022,321,10,537,521, 10,624,842, 10,751,277, 10,751,278, 10,751,279, 10,646,433, 10,729,644, 10,729,645, and 10,617,635) provides strong protection, our market opportunity would be limited if a generic manufacturer could obtain regulatory approval for another IV formulation of tramadol and commercialize it without infringing our patents.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, rendered unenforceable, or interpreted narrowly.

We may become involved in other types of legal proceedings related to our intellectual property that could result in the invalidation or unenforceability of our patents and could be expensive and time consuming, regardless of the outcome.

Any party can challenge the validity of our patents in post-grant proceedings at the PTAB, which include *inter partes* review and *post-grant* review proceedings. Although these proceedings are more limited, and therefore are often less expensive, than district court litigation, they can still require substantial resources. If the PTAB finds that our patents are unpatentable, we will be unable to enforce those patents against our competitors. Additionally, our competitors may bring other administrative challenges to our patents before the USPTO, including opposition, derivation, interference, *ex parte* reexamination, and *inter partes* reexamination proceedings. These proceedings may prevent our patent applications from issuing, or for patents that are already issued, an unsuccessful outcome will render the patent unenforceable.

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.

Our ability to develop, manufacture, market and potentially sell our product candidates or any other product candidates that we may license or acquire depends upon our ability to avoid infringing the proprietary rights of third parties. Numerous U.S. and foreign patents and pending patent applications, which are owned by third parties, exist in the general fields of pain treatment and neurologic disorder treatment and cover the use of numerous compounds and formulations in our targeted markets. Because of the uncertainty inherent in any patent or other litigation involving proprietary rights, we and our licensors may not be successful in defending intellectual property claims by third parties, which could have a material adverse effect on our results of operations. Regardless of the outcome of any litigation, defending the litigation may be expensive, time-consuming and distracting to management. In addition, because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that our product candidates may infringe. There could also be existing patents of which we are not aware that one of our product candidates may inadvertently infringe.

There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and biopharmaceutical industries generally. If a third party claims that we infringe on their patents or misappropriated their technology, we could face a number of issues, including:

- infringement and other intellectual property claims which, with or without merit, can be expensive and time consuming to litigate and can divert management's attention from our core business;
- substantial damages for past infringement which we may have to pay if a court decides that our product infringes on a competitor's patent;
- a court prohibiting us from selling or licensing our product unless the patent holder licenses the patent to us, which it would not be required to do;
- if a license is available from a patent holder, we may have to pay substantial royalties or grant cross licenses to our patents; and
- redesigning our processes so they do not infringe, which may not be possible or could require substantial funds and time.

We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property, including patent rights that are important or necessary to the development and potential commercialization of our product. It may be necessary for us to use the patented or proprietary technology of third parties to potentially commercialize our product, in which case we would be required to obtain a license from these third parties on commercially reasonable terms, or our business could be harmed, possibly materially.

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.

We are currently party to license agreements under which we acquired rights to develop and market IV Tramadol, BAER-101 and AJ201. The applicable license agreement for IV Tramadol will terminate on a product-by-product and country-by-country basis upon the expiration of the last licensed patent right, unless the agreement is earlier terminated. In addition to standard early termination

provisions, the License Agreement included provisions allowing early termination by: (i) Revogenex Ireland Ltd. ("Revogenex") if the FDA did not issue an approval or otherwise issues a "not approvable" notice for the NDA within 15 months after the NDA was filed with the FDA, although this termination right will be tolled if we are using commercially reasonable efforts in our negotiations with the FDA for approval and if we receive a "not approvable" notice, we will have a 15 month period to correct any issues and re-submit the NDA for approval, (ii) us if we reasonably determine prior to NDA approval that the development of IV Tramadol is not economically viable, or (iii) either Revogenex or us (provided we are using or have used commercially reasonable efforts to commercialize IV Tramadol) if, after the third anniversary date of the commercial launch, we fail to achieve annual net sales with respect to IV Tramadol of at least $20 million in any given calendar year, with certain exceptions.

Baergic is similarly party to two license agreements related to BAER-101, one with AstraZeneca AB and another with Cincinnati Children's Hospital Medical Center. Both license agreements were entered into in December 2019. Baergic acquired an exclusive license from AstraZeneca AB to patent and related intellectual property rights pertaining to its proprietary GABA-A 2,3 positive allosteric modulator, and also acquired from Cincinnati Children's Hospital Medical Center patent and related intellectual property rights pertaining to GABA inhibition for neurological disorders. Baergic is obligated to use commercially reasonable efforts to develop and commercialize the licensed products in the U.S. and European Union.

Finally, we licensed rights to AJ201 from AnnJi under a license agreement we entered into in February 2023. Under this license agreement, we 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 U.S. for the treatment of spinal and bulbar muscular atrophy, also known as Kennedy's Disease. The license is exclusive as to all oral forms of AJ201 for use in all indications (other than androgenetic alopecia and Alzheimer's disease) in the United States, Canada, the European Union, the United Kingdom and Israel. The license agreement also contains customary representations and warranties and provisions related to confidentiality, diligence, indemnification and intellectual property protection. If we fail to comply with the terms of this license agreement, we could lose rights to develop and market AJ201.

In the future, we may become party to licenses that are important for product development and potential commercialization. If we fail to comply with our obligations under current or future license and funding agreements, our counterparties may have the right to terminate these agreements, in which event we might not be able to develop, manufacture or market any product or utilize any technology that is covered by these agreements or may face other penalties under the agreements. Such an occurrence could materially and adversely affect the value of a product candidate being developed under any such agreement or could restrict our drug discovery activities. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology.

To the extent we operate in foreign jurisdictions, we may be exposed to increased risk associated with the potential theft of technology and intellectual property.

Our U.S. patents can be enforced against those who make, use, offer to sell, or sell our licensed patented inventions within the U.S., or against those who import our licensed patented inventions within the U.S. We may depend on foreign intellectual property rights to prevent competitors from manufacturing and selling our products outside of the U.S. without our authorization. Foreign laws and regulations may not protect our patent rights and trade secret rights to the same extent as U.S. law. It is also possible that we may be required to compromise protections or waive rights in order to conduct business in a foreign jurisdiction. Such restrictions may limit our ability to profitably compete in those markets.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

As is common in the biotechnology and pharmaceutical industry, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patent protection for our product candidates or future product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position, particularly where

we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We limit disclosure of such trade secrets where possible but we also seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who do have access to them, such as our employees, our licensors, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and may unintentionally or willfully disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. Moreover, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

General Risk Factors

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

Any potential future clinical trials may experience delays in patient enrollment, potentially due to prioritization of hospital resources toward the COVID-19 pandemic, or concerns among patients about participating in clinical trials during a public health emergency. During 2020 and 2021, the COVID-19 pandemic affected the operations of government entities, such as the FDA, as well as contract research organizations, third-party manufacturers, and other third-parties upon whom we rely. As a result of "shelter-in-place" orders, quarantines or similar orders or restrictions to control the spread of COVID-19, many companies, including our own, implemented work-from-home policies for their employees during 2020, 2021 and into 2022. The effects of these stay-at-home orders and work-from-home policies may be negatively impacting productivity, resulting in delays in our timelines. The extent of the impact on our operations depends in part on whether governments and businesses reinstate these restrictions as a result of a rising surge in COVID-19 cases or a new variant of the virus. These and similar disruptions in our operations could negatively impact our business, operating results and financial condition, however, as of the date of this Annual Report on Form 10-K, we have not experienced a significant impact on our business resulting from government restrictions on the movement of people, goods, and services.

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

Our results of operations and liquidity needs could be materially negatively affected by market fluctuations and economic downturn.

Our results of operations could be materially negatively affected by economic conditions generally, both in the United States and elsewhere around the world. Continuing concerns over inflation, energy costs, geopolitical issues, including the invasion of Ukraine by military forces of the Russian Federation, the availability and cost of credit, the U.S. mortgage market and residential real estate market in the United States have contributed to increased volatility and diminished expectations for the economy and the markets going forward. These factors, combined with volatile oil prices, declining business and consumer confidence and increased interest rate, have precipitated an economic recession and fears of a possible depression. Domestic and international equity markets continue to experience heightened volatility and turmoil. These events and the continuing market upheavals may have an adverse effect on us. In the event of a continuing market downturn, our results of operations could be adversely affected by those factors in many ways, including making it more difficult for us to raise funds if necessary, and our stock price may further decline.

We will continue to incur significant increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives.

We are a listed and traded public company. As a public company, we incur significant legal, accounting and other expenses under the Sarbanes-Oxley Act of 2002, as well as rules subsequently implemented by the SEC and the rules of the Nasdaq Stock Market, on which our common stock is listed. These rules impose various requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and appropriate corporate governance practices. Our management and other personnel have devoted and will continue to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly. For

example, these rules and regulations make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

The Sarbanes-Oxley Act of 2002 requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. As a result, we are required to periodically perform an evaluation of our internal controls over financial reporting to allow management to report on the effectiveness of those controls, as required by Section 404 of the Sarbanes-Oxley Act. However, while we remain a non-accelerated filer, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we have engaged in a process to document and evaluate our internal control over financial reporting. These efforts to comply with Section 404 and related regulations have required, and continue to require, the commitment of significant financial and managerial resources. While we anticipate maintaining the integrity of our internal controls over financial reporting and all other aspects of Section 404, we cannot be certain that a material weakness will not be identified when we test the effectiveness of our control systems in the future. If a material weakness is identified, we could be subject to sanctions or investigations by the SEC or other regulatory authorities, which would require additional financial and management resources, costly litigation or a loss of public confidence in our internal controls, which could have an adverse effect on the market price of our stock.

Our business and operations would suffer in the event of system failures.

Despite the implementation of security measures, our internal computer systems are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Any system failure, accident or security breach that causes interruptions in our operations could result in a material disruption of our drug development programs. For example, the loss of clinical trial data from completed clinical trials for our product candidates could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we may incur liability and the further development of our product candidates may be delayed.

The occurrence of a catastrophic disaster could damage our facilities beyond insurance limits or we could lose key data which could cause us to curtail or cease operations.

We are vulnerable to damage and/or loss of vital data from natural disasters, such as earthquakes, tornadoes, power loss, fire, health epidemics and pandemics, floods and similar events, as well as from accidental loss or destruction. If any disaster were to occur, our ability to operate our businesses could be seriously impaired. We have property, liability and business interruption insurance that may not be adequate to cover losses resulting from disasters or other similar significant business interruptions, and we do not plan to purchase additional insurance to cover such losses due to the cost of obtaining such coverage. Any significant losses that are not recoverable under our insurance policies could seriously impair our business, financial condition and prospects. Any of the aforementioned circumstances may also impede our employees' and consultants' abilities to provide services in-person and/or in a timely manner; hinder our ability to raise funds to finance our operations on favorable terms or at all; and trigger effectiveness of "force majeure" clauses under agreements with respect to which we receive goods and services, or under which we are obligated to achieve developmental milestones on certain timeframes. Disputes with third parties over the applicability of such "force majeure" clauses, or the enforceability of developmental milestones and related extension mechanisms in light of such business interruptions, may arise and may become expensive and time-consuming.

We may become involved in securities class action litigation that could divert management's attention and harm our business.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the common stock of biotechnology and pharmaceutical companies. These broad market fluctuations may cause the market price of our stock to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharmaceutical companies have experienced significant stock price volatility in recent years and due to the significant stock price decline we experienced following the announcement of the First CRL. We may become involved in this type of litigation in the future. Litigation often is expensive and diverts management's attention and resources, which could adversely affect our business.

Risks Pertaining to the Influence of Fortress

Fortress controls a voting majority of our common stock.

Pursuant to the terms of the Class A Preferred Stock held by Fortress, Fortress will be entitled to cast, for each share of Class A Preferred Stock held by Fortress, 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, or the "Class A Preferred Stock Ratio." Thus, Fortress 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, shall be entitled to appoint or elect the majority of our directors.

Accordingly, conflicts of interest may arise between Fortress and its affiliates, on the one hand, and us and our other stockholders, on the other hand. In resolving these conflicts of interests, Fortress may favor its own interests and the interests of its affiliates, over the interests of our other stockholders, which could cause a material adverse effect on our business, financial condition and results of operations.

Fortress has the right to receive a significant grant of shares of our common stock annually, which would result in the dilution of your holdings of common stock upon each grant, which could reduce their value.

Under the terms of the Amended and Restated Founders Agreement, which became effective September 13, 2016, Fortress is entitled to receive a grant of shares of our common stock equal to 2.5% of the gross amount of any equity or debt financing. Additionally, the holders of Class A Preferred Stock, as a class, are to receive an Annual Stock Dividend, payable in shares of common stock in an amount equal to 2.5% of our fully-diluted outstanding capital stock as of the business day immediately prior to the date such dividend is payable. Fortress currently owns all outstanding shares of Class A Preferred Stock. At our Annual Meeting of Stockholders held on June 13, 2018, the Company's stockholders approved an amendment to the Company's Third Amended and Restated Certificate of Incorporation, amending the Class A Preferred dividend payment date from February 17 to January 1 of each year. These potential future share issuances to Fortress and any other holder of Class A Preferred Stock will dilute your holdings in our common stock and, if our value has not grown proportionately over the prior year, would result in a reduction in the value of your shares. The Amended and Restated Founders Agreement has a term of 15 years and renews automatically for subsequent one-year periods unless terminated by Fortress or upon a Change in Control (as defined in the Amended and Restated Founders Agreement).

We might have received better terms from unaffiliated third parties than the terms we receive in our agreements with Fortress.

We entered into certain agreements with Fortress in connection with our separation from Fortress into an independent company, including the Management Services Agreement, or the "MSA," and the Founders Agreement, and entered into the Contribution Agreement with Fortress in May 2022. While we believe the terms of these agreements are reasonable, they might not reflect terms that would have resulted from arm's-length negotiations between unaffiliated third parties. The terms of the agreements relate to, among other things, payment of a royalty on product sales, the provision of employment and transition services and the contribution to us of a majority of the outstanding equity securities of Baergic previously held by Fortress. We might have received better terms from third parties because, among other things, third parties might have competed with each other to win our business.

The ownership by our executive officers and some of our directors of equity securities of Fortress and/or rights to acquire equity securities of Fortress might create, or appear to create, conflicts of interest.

Because of their current or former positions with Fortress, some of our executive officers and directors own shares of Fortress common stock and/or options to purchase shares of Fortress common stock. Their individual holdings of common stock and/or options to purchase common stock of Fortress may be significant compared to their total assets. Ownership by our directors and officers, after our separation from Fortress, of common stock and/or options to purchase common stock of Fortress create or might appear to create conflicts of interest when these directors and officers are faced with decisions that could have different implications for Fortress than for us. For instance, and by way of example, if there were to be a dispute between Fortress and us regarding the calculation of the royalty fee due to Fortress under the terms of the Founders Agreement, then certain of our officers and directors may have and will appear to have a conflict of interest with regard to the outcome of such dispute.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

Our corporate and executive office is located at 1111 Kane Concourse Suite 301, Bay Harbor Islands, FL 33154. We are not currently under a lease agreement at 1111 Kane Concourse, but we are provided access to this space by Fortress at no additional cost. We believe that our existing facilities are adequate to meet our current requirements. We do not own any real property.

Item 3. Legal Proceedings

To our knowledge, there are no legal proceedings pending against us, other than routine actions and administrative proceedings, and other actions not deemed material are not expected to have a material adverse effect on our financial condition, results of operations, or cash flows. In the ordinary course of business, however, the Company may be subject to both insured and uninsured litigation. Suits and claims may be brought against the Company by customers, suppliers, partners and/or third parties (including tort claims for personal injury arising from clinical trials of the Company's product candidates and property damage) alleging deficiencies in performance, breach of contract, etc., and seeking resulting alleged damages.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our common stock is listed on the Nasdaq Capital Market and trades under the symbol "ATXI".

Holders

As of March 28, 2023, there were approximately 5.9 million shares of common stock outstanding. The number of record holders of our common stock as of March 28, 2023 was 35.

Dividends

We have never paid or declared any cash dividends on our common stock, and we do not anticipate paying any cash dividends on our common stock in the foreseeable future. We intend to retain all available funds and any future earnings to fund the development and expansion of our business. Any future determination to pay dividends will be at the discretion of our board of directors and will depend upon a number of factors, including our results of operations, financial condition, future prospects, contractual restrictions, restrictions imposed by applicable law and other factors our board of directors deems relevant.

Equity Compensation Plans

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to "Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters."

Recent Sales of Unregistered Securities

Not applicable.

Description of Registrant's Securities to be Registered

Not applicable.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

Not applicable.

Item 6. Reserved

Item 7. Management's Discussion and Analysis of the Results of Operations

Forward-Looking Statements

Statements in the following discussion and throughout this report that are not historical in nature are "forward-looking statements." You can identify forward-looking statements by the use of words such as "expect," "anticipate," "estimate," "may," "will," "should," "intend," "believe," and similar expressions. Although we believe the expectations reflected in these forward-looking statements are reasonable, such statements are inherently subject to risk and we can give no assurances that our expectations will prove to be correct. Actual results could differ from those described in this report because of numerous factors, many of which are beyond our control. These factors include, without limitation, those described under Item 1A "Risk Factors." We undertake no obligation to update these forward-looking statements to reflect events or circumstances after the date of this report or to reflect actual outcomes. Please see "Forward-Looking Statements" at the beginning of this Form 10-K.

The following discussion of our financial condition and results of operations should be read in conjunction with our audited consolidated financial statements and the related notes thereto and other financial information appearing elsewhere in this Form 10-K. We undertake no obligation to update any forward-looking statements in the discussion of our financial condition and results of operations to reflect events or circumstances after the date of this report or to reflect actual outcomes.

Overview

Avenue Therapeutics, Inc. ("Avenue" or the "Company") is a specialty pharmaceutical company focused on the development and commercialization of therapies for the treatment of rare and neurologic diseases. Our 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.

AJ201

In February 2023, we announced that we entered into a license agreement (the "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 spinal and bulbar muscular atrophy ("SBMA"), also known as Kennedy's Disease.

Under the License Agreement, in exchange for exclusive rights to the intellectual property underlying the AJ201 product candidate, the Company will pay an initial cash license fee of $3.0 million, of which $2.0 million is payable within 60 days and $1 million payable within 180 days after the effective date of the License Agreement. The Company is also obligated to issue shares of its common stock under the Subscription Agreement (described below) and make additional payments over the course of the License Agreement including reimbursement payments of up to $10.8 million in connection with the product's Phase 1b/2a clinical trial.

In connection with the signing of the License Agreement, the Company agreed to issue 831,618 shares of its common stock to AnnJi (the "First Tranche Shares"), and then to issue an additional 276,652 shares of Common Stock upon enrollment of the eighth patient in the ongoing Phase 1b/2a SBMA clinical trial (the "Second Tranche Shares" and, together with the First Tranche Shares, the "Consideration Shares"). The license provided under the License Agreement is exclusive as to all oral forms of AJ201 for use in all indications (other than androgenetic alopecia and Alzheimer's disease) in the United States, Canada, the European Union, the United Kingdom and Israel. The License Agreement also contains customary representations and warranties and provisions related to confidentiality, diligence, indemnification and intellectual property protection. The Company will initially be obligated to obtain both clinical and commercial supply of AJ201 exclusively through AnnJi. The Company and AnnJi entered into a subscription agreement, dated as of February 28, 2023 (the "Subscription Agreement") that provides for the issuance of First Tranche Shares, which contains customary representations and warranties of the Company and AnnJi, respectively, and is subject to customary closing conditions. The Company and AnnJi will enter into a subsequent subscription agreement, in substantially the same form as the Subscription Agreement, with respect to the issuance of the Second Tranche Shares. Also in connection with execution of the License Agreement, the Company entered into a registration rights agreement (the "Registration Rights Agreement") with AnnJi. Pursuant to the Registration Rights Agreement, the Company will be required to file, on or prior to August 28, 2023, a registration statement with the U.S. Securities and Exchange Commission (the "SEC") to register the resale of the Consideration Shares.

IV Tramadol

On February 15, 2022, we had our Advisory Committee meeting with the FDA regarding IV Tramadol. 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.

We announced on March 8, 2023 that the Company would participate in a Type C meeting with the FDA on March 9, 2023 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

We recently expanded our business with the acquisition of Baergic Bio, Inc. ("Baergic") and its asset BAER-101, which would strategically align with Avenue's goals of building a rare and neurologic pipeline. On May 11, 2022, we entered into a stock contribution agreement (the "Contribution Agreement") with Fortress, pursuant to which Fortress agreed to transfer ownership of 100% of its shares (common and preferred) in Baergic to us. The acquisition was completed on November 8, 2022 and as a result, Baergic is currently a majority-controlled and owned private subsidiary company of Avenue.

Baergic is a clinical-stage pharmaceutical company founded in December 2019 that focuses on the development of pharmaceutical products for the treatment of neurologic disorders. Baergic's pipeline currently consists of a single compound, BAER-101, a novel α2/3–subtype-selective GABA A positive allosteric modulator ("PAM"). BAER-101 (formally known as AZD7325) was originally developed by AstraZeneca and has an established safety profile in early clinical trials including over 700 patients.

Under the Contribution Agreement, Fortress also agreed to assign to us certain intercompany agreements existing between Fortress and Baergic, including a Founders Agreement and Management Services Agreement. Consummation of the transactions contemplated by the Contribution Agreement was subject to the satisfaction of certain conditions precedent, including, inter alia: (i) the closing of an equity financing by the Company resulting in gross proceeds of no less than $7.5 million, (ii) the agreement by minority Avenue shareholder InvaGen Pharmaceuticals Inc. ("InvaGen") to (A) have 100% of its shares in us repurchased by us and (B) terminate certain of the agreements into which it entered with us and/or Fortress in connection with InvaGen's 2019 equity investment in us, which will eliminate certain negative consent rights of InvaGen over us and restore certain rights and privileges of Fortress in us (all upon terms to be agreed upon with InvaGen); and (iii) the sustained listing of our common stock on Nasdaq.

The Baergic transaction expands our development portfolio within neurologic diseases. Evaluation and negotiation of the Contribution Agreement was overseen, and execution of the Contribution Agreement was approved, by special committees at the Avenue and Fortress levels, both of which exclusively comprised independent and disinterested directors of the respective companies' boards.

Our net loss for the years ended December 31, 2022 and 2021 was approximately $3.6 million and $3.7 million, respectively. As of December 31, 2022, we had an accumulated deficit of approximately $80.6 million. Substantially all our net losses resulted from costs incurred in connection with our research and development program of IV Tramadol and from general and administrative costs associated with our operations.

We expect to continue to incur research and development costs and increased general and administration related costs and incur operating losses for at least the next several years as we continue the development of our product candidates.

We intend to obtain additional capital through the sale of debt or equity financings or other arrangements to fund our operations, research and development activity or regulatory approval activity; however, there can be no assurance that we will be able to raise the necessary capital under acceptable terms, if at all. The sale of additional equity may dilute existing stockholders and newly issued shares may contain senior rights and preferences compared to currently outstanding shares of our common stock. Issued debt securities may contain covenants and limit our ability to pay dividends or make other distributions to stockholders. If we are unable to obtain such additional financing, future operations would need to be scaled back or discontinued.

We are a majority-controlled subsidiary of Fortress. For related party transactions, see Note 4 to our audited consolidated financial statements included herein.

Avenue Therapeutics, Inc. was incorporated in Delaware on February 9, 2015. Our executive offices are located at 1111 Kane Concourse, Suite 301, Bay Harbor Islands, FL 33154. Our telephone number is (781) 652-4500, and our email address is info@avenuetx.com.

Recent Developments

Chief Executive Officer

On August 1, 2022, the Board approved the appointment of Dr. Alexandra MacLean as Chief Executive Officer of the Company. With the appointment of Dr. MacLean as the new Chief Executive Officer, Mr. David Jin ended his term as interim Chief Executive Officer and will continue his responsibilities as Interim Chief Financial Officer and Chief Operating Officer of the Company.

NASDAQ Deficiency Letter

On May 24, 2022, we received a deficiency letter (the "Nasdaq Letter") from the Listing Qualifications Department of The Nasdaq Stock Market LLC ("Nasdaq"), notifying us that we are not in compliance with Nasdaq Listing Rule 5550(b)(1), which requires us to maintain a minimum of $2,500,000 in stockholders' equity for continued listing on The Nasdaq Capital Market (the "Stockholders' Equity Requirement"), nor in compliance with either of the alternative listing standards, market value of listed securities of at least $35 million or net income of $500,000 from continuing operations in the most recently completed fiscal year, or in two of the three most recently completed fiscal years. Our failure to comply with the Stockholders' Equity Requirement was based on the filing of our Quarterly Report on Form 10-Q for the quarter ended March 31, 2022, reporting the stockholders' equity of $1,159,000. Pursuant to the Nasdaq Letter, we had 45 calendar days from the date of the Nasdaq Letter to submit a plan to regain compliance. On July 8, 2022, we submitted a compliance plan (the "Compliance Plan") to Nasdaq.

On August 9, 2022, we received written notice (the "Notice") from Nasdaq, stating that the Nasdaq has determined that we have not complied with the Nasdaq Listing Rule 5550(a)(2), which requires us to maintain a minimum bid price of our common stock be at least $1.00 per share (the "Minimum-Bid Price Requirement"), or the Stockholders' Equity Requirement. The Notice indicated that our common stock would be suspended from trading on Nasdaq unless we request a hearing before an independent hearings panel (the "Panel") by August 16, 2022.

Additionally, as previously disclosed on February 8, 2022, we received a letter from the Regulations Department of The Nasdaq Stock Market LLC indicating that the closing bid price of our common stock has been below $1.00 per share for 30 consecutive business days, and that, therefore, we are not in compliance with the Minimum-Bid Price Requirement for continued listing on The Nasdaq Capital Market.

We timely requested a hearing before the Panel, which took place on September 22, 2022. On September 29, 2022, the Panel issued a decision granting our request for continued listing on Nasdaq, through October 31, 2022, to demonstrate compliance with the Stockholders' Equity Requirement, and through October 6, 2022 to satisfy the Minimum Bid Price Requirement.

On October 18, 2022, we were formally notified by Nasdaq that we have evidenced compliance with the Minimum-Bid Price Requirement and the Stockholders' Equity Requirement for continued listing on The Nasdaq Capital Market, as set forth in Nasdaq Listing Rules 5550(a)(2) and 5550(b)(1), respectively. Accordingly, the listing matter has been closed.

Reverse Stock Split

On July 25, 2022, the holders of a majority of the voting power of our capital stock executed a written consent approving a grant of discretionary authority to our board of directors (the "Board") to, without further stockholder approval, (i) effect a reverse stock split of our issued and outstanding common stock within a range of between 10-for-1 and 20-for-1 (with the Board being authorized to determinate the exact ratio) (the "Reverse Stock Split") and (ii) reduce the number of our authorized shares of common stock from 50,000,000 to 20,000,000 (the "Authorized Share Reduction") by filing an amendment (the "Amendment") to our Third Amended and Restated Certificate of Incorporation with the Secretary of State of the State of Delaware. The written consent was signed by the holders of 9,423,429 shares of our common stock and 250,000 shares of our Class A Preferred Stock. Each share of common stock entitles the holder thereof to one vote on all matters submitted to stockholders and each share of Class A Preferred Stock has the voting power of 1.1 times (A) the number of outstanding shares of common stock plus (B) the whole shares our common stock into which the outstanding shares of Class A Preferred Stock are convertible, divided by the number of outstanding shares of Class A Preferred Stock, or 99 votes per share as of July 25, 2022. Accordingly, the holders of approximately 73% of the voting power of our capital stock as of July 25, 2022 signed the written consent approving the Reverse Stock Split, the Authorized Share Reduction and the Amendment. The Board also approved the Reverse Stock Split, the Authorized Share Reduction and the Amendment.

The Reverse Stock Split was effective on September 23, 2022 upon filing of the Amendment with the Secretary of State of Delaware, which date was at least twenty (20) days following the mailing of the information statement. Under the Amendment, the number of authorized shares of common stock immediately after the Reverse Stock Split ("New Common Stock") was simultaneously reduced from 50,000,000 to 20,000,000 shares. All share and per share information has been retroactively adjusted to give effect to the Reverse Stock Split for all periods presented, unless otherwise indicated.

As a result of the Reverse Stock Split, every 15 shares of common stock outstanding immediately prior to the effectiveness of the Reverse Stock Split were combined and converted into one share of New Common Stock without any change in the par value per share. No fractional shares were issued in connection with the Reverse Stock Split. Stockholders who would otherwise be entitled to a fraction of one share of New Common Stock as a result of the Reverse Stock Split instead received an amount in cash equal to such fraction multiplied by the closing sale price of common stock on the Nasdaq Capital Market on September 22, 2022, as adjusted for the Reverse Stock Split.

October 2022 Public Offering

On October 6, 2022, we entered into an Underwriting Agreement (the "Underwriting Agreement") with Aegis Capital Corp., as underwriter (the "Underwriter"), related to our underwritten public offering (the "October 2022 Offering") of 2,652,065 units ("Units") and 984,300 pre-funded units ("Pre-funded Units"). Each Unit consisted of one share (a "Share") of our common stock, and one warrant to purchase one share of our common stock (each, a "Warrant" and, collectively, the "Warrants"), and each Pre-funded Unit consisted of one pre-funded warrant to purchase one share of common stock (each, a "Pre-funded Warrant" and collectively, the "Pre-funded Warrants") and one Warrant. The Units were sold at a price of $3.30 per Unit, and the Pre-Funded Units were sold at a price of $3.2999 ($3.30 less $0.0001, the exercise price of the Pre-funded Warrants).

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

We received net proceeds from the Offering of $10.3 million, after deducting underwriting discounts and commissions and estimated offering expenses payable us.

InvaGen Share Repurchase

In connection with the closing of the Offering, on October 11, 2022, we consummated the transactions contemplated by the Share Repurchase Agreement with InvaGen, pursuant to which we repurchased 100% of the shares in the Company held by InvaGen (the

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

January 2023 Registered Offering and Private Placement

On January 27, 2023, we entered into a Securities Purchase Agreement (the "Registered Purchase Agreement") with a single institutional accredited investor, pursuant to which we agreed to issue and sell (i) 448,000 shares (the "Shares") of our common stock at a price per Share of $1.55, and (ii) pre-funded warrants (the "Pre-funded Warrants") to purchase 1,492,299 shares of common stock, at a price per Pre-funded Warrant equal to the price per Share, less $0.001 (the "Registered Offering"). The Pre-funded Warrants have an exercise price of $0.001 per share, became exercisable upon issuance and remain exercisable until exercised in full. We received approximately $3.0 million in gross proceeds from the Registered Offering, before deducting placement agency fees and estimated offering expenses.

On January 27, 2023, we also entered into a Securities Purchase Agreement (the "PIPE Purchase Agreement") with the same institutional accredited investor for a private placement offering ("Private Placement") of warrants (the "PIPE Warrants") to purchase 1,940,299 shares of common stock. Pursuant to the PIPE Purchase Agreement, we agreed to issue and sell the PIPE Warrants at an offering price of $0.125 per PIPE Warrant to purchase one share of common stock. The PIPE Warrants have an exercise price of $1.55 per share (subject to adjustment as set forth in the PIPE Warrants), are exercisable six months after issuance and will expire three years from the date on which the PIPE Warrants become exercisable. The PIPE 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 the Registered Offering. The gross proceeds to us from the Private Placement, before deducting placement agent fees and other estimated offering expenses payable by us, were approximately $0.24 million.

In connection with the PIPE Purchase Agreement, we entered into a registration rights agreement (the "Registration Rights Agreement") with the investor. Pursuant to the Registration Rights Agreement, we will be required to file, on or prior to April 10, 2023 (the "Filing Date"), a resale registration statement (the "Resale Registration Statement") with the SEC to register the resale of the shares issuable upon exercise of the PIPE Warrants. Pursuant to the Registration Rights Agreement, the Resale Registration Statement must be declared effective by the SEC within 15 days after the Filing Date or 45 days following the Filing Date if the Resale Registration Statement is reviewed by the SEC. We will be obligated to pay certain liquidated damages to the investor if we fail to file the resale registration statement when required, if the Resale Registration Statement is not declared effective by the SEC when required under the Registration Rights Agreement, or if we fail to maintain the effectiveness of the Resale Registration Statement.

Critical Accounting Policies and Use of Estimates

Our discussion and analysis of our financial condition and results of operations are based on our audited consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States ("U.S. GAAP"). The preparation of these audited consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our audited consolidated financial statements. On an ongoing basis, we evaluate our estimates and judgments, including those related to accrued expenses and stock-based compensation. We base our estimates on historical experience, known trends and events and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

Research and Development

Research and development costs are expensed as incurred. Advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made. Upfront and milestone payments due to third parties that perform research and development services on our behalf will be expensed as services are rendered or when the milestone is achieved. Costs incurred in obtaining technology licenses are charged to research and development expense if the technology licensed has not reached technological feasibility and has no alternative future use.

Research and development costs primarily consist of personnel related expenses, including salaries, benefits, travel, and other related expenses, stock-based compensation, payments made to third parties for license and milestone costs related to in-licensed products and technology, payments made to third party contract research organizations for preclinical and clinical studies, investigative sites for clinical trials, consultants, the cost of acquiring and manufacturing clinical trial materials, costs associated with regulatory filings and patents, laboratory costs and other supplies.

Costs incurred in obtaining technology licenses are charged to research and development expense if the technology licensed has not reached commercial feasibility and has no alternative future use. The licenses purchased by us require substantial completion of research and development, regulatory and marketing approval efforts in order to reach commercial feasibility and has no alternative future use. Accordingly, the total purchase price for the licenses acquired are reflected as research and development.

Stock-Based Compensation

We expense stock-based compensation to employees, consultants and board members over the requisite service period based on the estimated grant-date fair value of the awards. Stock-based awards with graded-vesting schedules are recognized on a straight-line basis over the requisite service period for each separately vesting portion of the award.

The assumptions used in calculating the fair value of stock-based awards represent management's best estimates and involve inherent uncertainties and the application of management's judgment.

Warrant Liabilities

We have issued freestanding warrants to purchase shares of our common stock in connection with financing activities. Our outstanding common stock warrants issued in connection with the equity financing completed in 2022 are classified as liabilities in the consolidated balance sheet as they contain terms for redemption of the underlying security that are outside our control. We use the Monte Carlo option pricing model to value warrants, which requires management to estimate inputs including expected volatility and expected term, and is most significantly impacted by our common stock price. These inputs are inherently subjective and require significant analysis and judgment to develop. The fair value of all warrants is re-measured at each financial reporting date with any changes in fair value being recognized in change in fair value of warrant liabilities, a component of other income (expense), in the consolidated statements of operations and comprehensive income (loss). We will continue to re-measure the fair value of the warrant liabilities until exercise or expiration of the related warrant.

Income Taxes

No income tax expense or benefit was recognized in the accompanying audited consolidated financial statements. Our deferred tax assets are comprised primarily of net operating loss carryforwards. We maintain a full valuation allowance on our deferred tax assets since we have not yet achieved sustained profitable operations. As a result, we have not recorded any income tax benefit since our inception.

Results of Operations

Comparison of the Years Ended December 31, 2022 and 2021

($ in thousands)	For The Years Ended December 31, 2022	2021
Operating expenses:		
Research and development	$ 2,698	$ 1,254
General and administrative	5,345	2,484
Loss from operations	(8,043)	(3,738)
Interest income	(20)	(7)
Financing costs - warrant liabilities	1,160	—
Change in fair value of warrant liabilities	(5,580)	—
Net Loss	**$ (3,603)**	**$ (3,731)**
Net loss attributable to non-controlling interests	**51**	—
Net Loss attributable to common stockholders	**$ (3,552)**	$ **(3,731)**

Research and Development Expenses

For the years ended December 31, 2022 and 2021, research and development expenses were $2.7 million and $1.3 million, respectively. The $1.4 million increase primarily reflects an increase of $0.8 million due advisory committee preparation and costs, $0.2 million in bonus costs, $0.3 million in acquired license costs and $0.1 million in non-cash stock compensation costs.

We expect our research and development activities to continue as we attempt to gain regulatory approval for IV Tramadol and pursue continued development of AJ201 and BAER-101, reflecting costs associated with the following:

- employee-related expenses;
- license fees and milestone payments related to in-licensed product and technology;
- expenses incurred under agreements with contract research organizations, investigative sites and consultants that conduct our clinical trials;
- the cost of acquiring and manufacturing clinical trial materials; and
- costs associated with non-clinical activities, and regulatory approvals.

General and Administrative Expenses

General and administrative expenses consist principally of professional fees for legal and consulting services, market research, personnel-related costs, public reporting company related costs and other general operating expenses not otherwise included in research and development expenses. We expect our general and administrative costs to continue as we seek potential regulatory approval and potential commercialization of our product candidates.

For the years ended December 31, 2022 and 2021, general and administrative expenses were $5.3 million and $2.5 million, respectively. The $2.8 million increase primarily reflects increases of $2.6 million in consulting and professional fees and $0.3 million in non-cash stock compensation costs partially offset by a decrease of $0.1 million in personnel costs.

Interest Income

Interest income was $20,000 and $7,000 for the years ended December 31, 2022 and 2021, respectively. The increase in interest income was due to increased interest rates and cash and cash equivalents.

Financing costs – warrant liabilities

Financing costs of our warrant liabilities reflect an allocation of total financing costs associated with the public offering in October 2022, on the basis of the fair value of the warrant liabilities as compared to the total proceeds received by the Company.

Change in fair value of warrant liability

Change in the estimated fair value of warrant liabilities is comprised of the fair value remeasurement of the liabilities associated with the October 2022 Public Offering. We account for warrants as either equity-classified or liability-classified instruments based on an assessment of the warrant's specific terms and applicable authoritative guidance in ASC 480 and ASC 815. The assessment considers whether the warrants are freestanding financial instruments pursuant to ASC 480, meet the definition of a liability pursuant to ASC 480, and whether the warrants meet all of the requirements for equity classification under ASC 815, including whether the warrants are indexed to the Company's own common stock, among other conditions for equity classification. This assessment, which requires the use of professional judgment, is conducted at the time of warrant issuance and as of each subsequent quarterly period end date while the warrants are outstanding.

For issued or modified warrants that meet all of the criteria for equity classification, the warrants are required to be recorded as a component of additional paid-in capital at the time of issuance. For issued or modified warrants that do not meet all the criteria for equity classification, the warrants are required to be recorded at their initial fair value on the date of issuance, and each balance sheet date thereafter. Changes in the estimated fair value of the warrants are recognized as a non-cash gain or loss on the consolidated statements of operations. The fair value of the warrants was estimated using a Monte Carlo simulation approach (see Note 2 to our audited consolidated financial statements included herein).

Liquidity and Capital Resources

Cash Flows for the Years Ended December 31, 2022 and 2021

($ in thousands)	For The Years Ended December 31, 2022	2021
Total cash and cash equivalents (used in)/provided by:		
Operating activities	$ (7,596)	$ (3,750)
Investing activities	—	—
Financing activities	10,541	4,381
Net increase/(decrease) in cash and cash equivalents	$ 2,945	$ 631

Operating Activities

Net cash used in operating activities was approximately $7.6 million for the year ended December 31, 2022, primarily comprised of our $3.6 million net loss and $5.6 million reduction in fair value of the warrant liability, partially offset by $0.7 million in share-based compensation, $0.5 million of common shares issuable and $0.4 million change in operating assets and liabilities.

Net cash used in operating activities was approximately $3.8 million for the year ended December 31, 2021, primarily comprised of our $3.7 million net loss and decrease in operating assets and liabilities of $0.5 million, partially offset by $0.4 million in share-based compensation.

Investing Activities

None.

Financing Activities

Net cash provided by financing activities for the year ended December 31, 2022 was $10.5 million, primarily related to $11.5 million in proceeds of our issuance of shares pursuant to our underwritten public offering in October 2022 and $0.1 million proceeds from exercise of warrants, partially offset by the $1.1 million repurchase of common shares of the Company from InvaGen.

Net cash provided by financing activities for the year ended December 31, 2021 was $4.4 million which was from the proceeds of our issuance of shares pursuant to our two underwritten public offerings in November and December 2021.

Recently Adopted Accounting Standards

See Note 2 to our audited consolidated financial statements included herein for a full description of recent accounting pronouncements including the respective expected dates of adoption and expected effects on results of operations and financial condition.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk.

We are a smaller reporting company as defined by Rule 12b-2 of the Exchange Act and are not required to provide the information otherwise required under this item.

Item 8. Financial Statements and Supplementary Data.

The information required by this Item is set forth in our audited consolidated financial statements and notes thereto beginning at page F-1 of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

Not applicable.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures. As of December 31, 2022, management carried out, under the supervision and with the participation of our principal executive officer and principal financial officer, an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act). Our disclosure controls and procedures are designed to provide reasonable assurance that information we are required to disclose in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in applicable rules and forms. Based upon that evaluation, our principal executive officer and principal financial officer concluded that, as of December 31, 2022, our disclosure controls and procedures were effective.

Management's Report on Internal Control over Financial Reporting. Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rule 13a-15(f) or Rule 15d-15(f) under the Exchange Act). Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, our management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission, known as COSO, in Internal Control-Integrated Framework (2013). Our management has concluded that, as of December 31, 2022, our internal control over financial reporting was effective based on these criteria.

Changes in Internal Control Over Financial Reporting. There were no changes in our internal control over financial reporting during the most recent fiscal quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Limitations on the Effectiveness of Controls. Our management, including our principal executive officer and principal financial officer, does not expect that our disclosure controls and procedures or our internal control over financial reporting will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within our company have been detected.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not Applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item is incorporated herein by reference from our Proxy Statement for our upcoming 2023 Annual Meeting of Stockholders.

Item 11. Executive Compensation

The information required by this Item is incorporated herein by reference from our Proxy Statement for our upcoming 2023 Annual Meeting of Stockholders.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this Item is incorporated herein by reference from our Proxy Statement for our upcoming 2023 Annual Meeting of Stockholders.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this Item is incorporated herein by reference from our Proxy Statement for our upcoming 2023 Annual Meeting of Stockholders.

Item 14. Principal Accounting Fees and Services

The information required by this Item is incorporated herein by reference from our Proxy Statement for our upcoming 2023 Annual Meeting of Stockholders.

PART IV

Item 15. Exhibits and Consolidated Financial Statement Schedules

(a) Consolidated Financial Statements.

The following consolidated financial statements are filed as part of this report:

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(b) Exhibits.

Exhibit No.	Description
3.1	Third Amended and Restated Certificate of Incorporation of Avenue Therapeutics, Inc., filed as Exhibit 3.1 to Form 8-K filed on June 27, 2017 (File No. 001-38114) and incorporated herein by reference.
3.2	Certificate of Amendment of the Third Amended and Restated Certificate of Incorporation of Avenue Therapeutics, Inc., filed as Exhibit 3.1 to Form 10-Q filed on August 14, 2018 (File No. 001-38114) and incorporated herein by reference.
3.3	Certificate of Amendment of the Third Amended and Restated Certificate of Incorporation of Avenue Therapeutics, Inc., filed as Exhibit 3.1 to Form 8-K filed on September 22, 2022 (File No. 001-38114) and incorporated herein by reference.
3.4	Certificate of Amendment of the Third Amended and Restated Certificate of Incorporation of Avenue Therapeutics, Inc., filed as Exhibit 3.1 to Form 8-K filed on February 1, 2023 (File No. 001-38114) and incorporated herein by reference.
3.5	Second Amended and Restated Bylaws of Avenue Therapeutics, Inc., filed as Exhibit 3.1 to Form 8-K filed on February 10, 2023 (File No. 000-38114) and incorporated herein by reference.
4.1	Specimen certificate evidencing shares of Common Stock, filed as Exhibit 4.1 to Form 10-12G filed on January 12, 2017 (File No. 000-55556) and incorporated herein by reference.
4.2	Form of warrant agreement, filed as Exhibit 4.2 to Form 10-12G filed on January 12, 2017 (File No. 000-55556) and incorporated herein by reference.
4.3	Description of Securities of Avenue Therapeutics, Inc.*
4.4	Form of Warrant, filed as Exhibit 4.1 to Form 8-K filed on October 12, 2022 (File No. 001-38114) and incorporated herein by reference.
4.5	Form of Pre-funded Warrant, filed as Exhibit 4.2 to Form 8-K filed on October 12, 2022 (File No. 001-38114) and incorporated herein by reference.
4.6	Form of Pre-funded Warrant (Registered Offering), filed as Exhibit 10.3 to Form 8-K filed on February 1, 2023 (File No. 001-38114) and incorporated herein by reference.
4.7	Form of PIPE Warrant (PIPE), filed as Exhibit 10.4 to Form 8-K filed on February 1, 2023 (File No. 001-38114) and incorporated herein by reference.
10.1	Asset Transfer and License Agreement between Fortress Biotech, Inc. and Revogenex Ireland Limited dated February 17, 2015, filed as Exhibit 10.1 to Form 10-12G/A filed on March 13, 2017 (File No. 000-55556) and incorporated herein by reference.**
10.2	First Amendment to Asset Transfer and License Agreement between Fortress Biotech, Inc. and Revogenex Ireland Limited dated June 23, 2016, filed as Exhibit 10.11 to Form 10-12G/A filed on March 13, 2017 (File No. 000-55556) and incorporated herein by reference.
10.3	Second Amendment to Asset Transfer and License Agreement between Fortress Biotech, Inc. and Revogenex Ireland Limited dated May 4, 2017, filed as Exhibit 10.3 to Form S-1/A filed on May 22, 2017 (File No. 333-217552) and incorporated herein by reference.
10.4	Amended and Restated Founders Agreement between Fortress Biotech, Inc. and Avenue Therapeutics, Inc. dated September 13, 2016, filed as Exhibit 10.2 to Form 10-12G filed on January 12, 2017 (File No. 000-55556) and incorporated herein by reference.
10.5	Management Services Agreement between Fortress Biotech, Inc. and Avenue Therapeutics, Inc. effective as of February 17, 2015, filed as Exhibit 10.5 to Form 10-12G filed on January 12, 2017 (File No. 000-55556) and incorporated herein by reference.

10.6	Employment Agreement with Dr. Lucy Lu, MD, dated June 10, 2015, filed as Exhibit 10.6 to Form 10-12G filed on January 12, 2017 (File No. 000-55556) and incorporated herein by reference.#
10.7	Avenue Therapeutics, Inc. 2015 Incentive Plan, filed as Exhibit 10.7 to Form 10-12G filed on January 12, 2017 (File No. 000-55556) and incorporated herein by reference.#
10.8	Consulting Agreement with Dr. Scott A. Reines, dated July 22, 2015, filed as Exhibit 10.8 to Form 10-12G filed on January 12, 2017 (File No. 000-55556) and incorporated herein by reference.#
10.9	First Amendment to Consulting Agreement with Dr. Scott A. Reines, dated January 25, 2016, filed as Exhibit 10.9 to Form 10-12G filed on January 12, 2017 (File No. 000-55556) and incorporated herein by reference.#
10.10	Second Amendment to Consulting Agreement with Dr. Scott A. Reines, dated August 2, 2016, filed as Exhibit 10.10 to Form 10-12G/A filed on March 13, 2017 (File No. 000-55556) and incorporated herein by reference.#
10.11	Third Amendment to Consulting Agreement with Dr. Scott A. Reines, dated February 28, 2017, filed as Exhibit 10.12 to Form 10-12G/A filed on March 13, 2017 (File No. 000-55556) and incorporated herein by reference.#
10.12	Stockholders Agreement, dated as of November 12, 2018, by and between Avenue Therapeutics, Inc., Fortress Biotech, Inc., Dr. Lucy Lu, M.D. and InvaGen Pharmaceuticals Inc., incorporated herein by reference from the Company's Form 8-K filed on November 14, 2018.
10.13	First Amendment to Executive Employment Agreement, dated as of November 12, 2018, by and between Avenue Therapeutics, Inc. and Dr. Lucy Lu, M.D., incorporated herein by reference from the Company's Form 8-K filed on November 14, 2018.#
10.14	Stock Contribution Agreement between Avenue Therapeutics, Inc. and Fortress Biotech, Inc., dated May 11, 2022, filed as Exhibit 10.1 to Form 10-Q filed on August 15, 2022 (File No. 001-38114) and incorporated herein by reference.
10.15	Underwriting Agreement, dated October 6, 2022, by and between Avenue Therapeutics, Inc. and Aegis Capital Corp., filed as Exhibit 1.1 to Form 8-K filed on October 12, 2022 (File No. 001-38114) and incorporated herein by reference.
10.16	Warrant Agent Agreement, dated October 6, 2022, by and between Avenue Therapeutics, Inc. and VStock Transfer, LLC, filed as Exhibit 4.1 to Form 8-K filed on October 12, 2022 (File No. 001-38114) and incorporated herein by reference.
10.17	Form of Securities Purchase Agreement (Registered Offering), dated January 27, 2023, by and among Avenue Therapeutics, Inc. and the purchaser party thereto, filed as Exhibit 10.1 to Form 8-K filed on February 1, 2023 (File No. 001-38114) and incorporated herein by reference.
10.18	Form of Securities Purchase Agreement (PIPE), dated January 27, 2023, by and among Avenue Therapeutics, Inc. and the purchaser party thereto, filed as Exhibit 10.2 to Form 8-K filed on February 1, 2023 (File No. 001-38114) and incorporated herein by reference.
10.19	Form of Registration Rights Agreement, dated January 27, 2023, by and among Avenue Therapeutics, Inc. and the purchaser party thereto, filed as Exhibit 10.5 to Form 8-K filed on February 1, 2023 (File No. 001-38114) and incorporated herein by reference.
10.20	Placement Agent Agreement entered into by and between Avenue Therapeutics, Inc. and Aegis Capital Corp., dated January 27, 2023, filed as Exhibit 10.7 to Form 8-K filed on February 1, 2023 (File No. 001-38114) and incorporated herein by reference.
16.1	Letter from BDO USA, LLP, filed as Exhibit 16.1 to Form 8-K filed on January 25, 2023 (File No. 001-38114) and incorporated herein by reference
21.1	Subsidiaries of Avenue Therapeutics, Inc.*

23.1	Consent of Independent Registered Public Accounting Firm, KPMG LLP.
23.2	Consent of Independent Registered Public Accounting Firm, BDO USA, LLP.
31.1	Certification of Principal Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.*
31.2	Certification of Principal Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.*
32.1	Certification of Principal Executive Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.*
32.2	Certification of Principal Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.*
101	The following financial information from Avenue Therapeutics, Inc.'s Annual Report on Form 10-K for the year ended December 31, 2022, formatted in XBRL (eXtensible Business Reporting Language): (i) Balance Sheets, (ii) Statement of Operations, (iii) Statement of Stockholders' Equity, (iv) Statements of Cash Flows, and (v) the Notes to Financial Statements

* Filed herewith.
** Subject to a request for confidential treatment.
# Management contract or compensatory plan.

Item 16. Form 10-K Summary

None.

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Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
Avenue Therapeutics, Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheet of Avenue Therapeutics, Inc. and subsidiary (the Company) as of December 31, 2022, the related consolidated statements of operations, stockholders' equity, and cash flows for the year then ended, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022, and the results of its operations and its cash flows for the year then ended, in conformity with U.S. generally accepted accounting principles.

We also have audited the adjustments to the 2021 consolidated financial statements to retrospectively apply the change in accounting due to the reverse stock split, as described in Note 1. In our opinion, such adjustments are appropriate and have been properly applied. We were not engaged to audit, review, or apply any procedures to the 2021 consolidated financial statements of the Company other than with respect to the adjustments and, accordingly, we do not express an opinion or any other form of assurance on the 2021 consolidated financial statements taken as a whole.

Going Concern

The accompanying consolidated financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the consolidated financial statements, 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 its ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 1. The consolidated financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audit included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks.

Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audit provides a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the consolidated financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of a critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Valuation of warrant liability

As discussed in Notes 2 and 7 to the consolidated financial statements, the Company accounts for certain warrants issued in October 2022 as a liability. At October 11, 2022, the issuance date, and December 31, 2022, the Company recorded a warrant liability of $8.3 million and $2.6 million, respectively. The Company estimated the fair value of the warrant liability at issuance and re-measures the liability at each financial reporting date with any changes in fair value being recognized in change in fair value of warrant liabilities, a component of other income (expense). The Company used a Monte Carlo simulation approach to value the warrants. Key inputs included expected volatility, expected term, the risk-free interest rate, expected dividend yield, and the Company's common stock price.

We identified the evaluation of the fair value of the warrant liability as of October 11, 2022 and December 31, 2022 as a critical audit matter. A high degree of auditor judgment and specialized skills and knowledge were required in the evaluation of the estimated fair values due to the degree of subjectivity associated with the expected volatility assumptions and their sensitivity to variation.

The following are the primary procedures we performed to address this critical audit matter. We evaluated the design of an internal control over the Company's valuation process, including the determination of the expected volatility assumption. We assessed the reasonableness of the fair value of the warrant liability by involving valuation professionals with specialized skills and knowledge, who assisted in developing an independent range of the fair value of the warrant liability as of October 11, 2022 and December 31, 2022, including volatility assumptions that were independently developed in consideration of historical and implied share price volatility information. We compared these independently developed ranges to the respective fair value of the warrant liability recorded by the Company as of October 11, 2022 and December 31, 2022.

KPMG LLP

We have served as the Company's auditor since 2022.

New York, New York
March 31, 2023

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

Stockholders and Board of Directors
Avenue Therapeutics, Inc.
New York, NY

Opinion on the Financial Statements

We have audited, before the effects of the adjustments to retrospectively apply the reverse stock split described in Note 1, the accompanying balance sheet of Avenue Therapeutics, Inc. (the "Company") as of December 31, 2021, the related statements of operations, stockholders' equity, and cash flows for the year then ended, and the related notes (collectively referred to as the "financial statements"). The 2021 financial statements before the effects of the adjustments discussed in Note 1 are not presented herein. In our opinion, the financial statements, before the effects of the adjustments to retrospectively apply the reverse stock split described in Note 1, present fairly, in all material respects, the financial position of the Company at December 31, 2021, and the results of its operations and its cash flows for the year then ended, in conformity with accounting principles generally accepted in the United States of America.

We were not engaged to audit, review, or apply any procedures to the adjustments to retrospectively apply the reverse stock split described in Note 1 and, accordingly, we do not express an opinion or any other form of assurance about whether such adjustments are appropriate and have been properly applied. Those adjustments were audited by KPMG LLP.

Going Concern Uncertainty

The accompanying financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the financial statements, the Company has suffered recurring losses from operations and has a capital deficiency that raise substantial doubt about its ability to continue as a going concern. Management's plans in regard to these matters are also described in Note 1. The financial statements do not include any adjustments that might result from the outcome of this uncertainty.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audit we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audit included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audit also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audit provides a reasonable basis for our opinion.

/s/ BDO USA, LLP

We have served as the Company's auditor from 2016 to 2022.

New York, NY
March 25, 2022

AVENUE THERAPEUTICS, INC.
Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	December 31, 2022	December 31, 2021
ASSETS		
Current assets:		
Cash and cash equivalents	$ 6,708	$ 3,763
Other receivables - related party	—	90
Prepaid expenses and other current assets	137	107
Total assets	**$ 6,845**	**$ 3,960**
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable and accrued expenses	$ 949	$ 451
Accounts payable and accrued expenses - related party	21	58
Warrant liability	2,609	—
Total current liabilities	3,579	509
		—
Total liabilities	3,579	509
Commitments and Contingencies		
Stockholders' equity		
Preferred stock ($0.0001 par value), 2,000,000 shares authorized		
Class A Preferred stock, 250,000 shares issued and outstanding as of December 31, 2022 and 2021, respectively	—	—
Common stock ($0.0001 par value), 20,000,000 shares authorized		
Common shares, 4,773,841 and 1,405,959 shares issued and outstanding as of December 31, 2022 and 2021, respectively	—	—
Additional paid-in capital	84,456	80,450
Accumulated deficit	(80,551)	(76,999)
Total stockholders' equity attributed to the Company	3,905	3,451
Non-controlling interests	(639)	—
Total stockholders' equity	3,266	3,451
Total liabilities and stockholders' equity	**$ 6,845**	**$ 3,960**

The accompanying notes are an integral part of these consolidated financial statements.

AVENUE THERAPEUTICS, INC.
Consolidated Statements of Operations
(In thousands, except share and per share amounts)

	For the Years Ended	
	December 31, 2022	December 31, 2021
Operating expenses:		
Research and development	$ 2,698	$ 1,254
General and administrative	5,345	2,484
Loss from operations	(8,043)	(3,738)
Interest income	(20)	(7)
Financing costs – warrant liabilities	1,160	—
Change in fair value of warrant liabilities	(5,580)	—
Net loss	**$ (3,603)**	**$ (3,731)**
Net loss attributable to non-controlling interests	51	—
Net loss attributable to common stockholders	**$ (3,552)**	**$ (3,731)**
Net loss per common share attributable to common stockholders, basic and diluted	$ (1.63)	$ (3.29)
Weighted average number of common shares outstanding, basic and diluted	2,185,159	1,133,170

The accompanying notes are an integral part of these consolidated financial statements.

AVENUE THERAPEUTICS, INC.
Consolidated Statements of Changes in Stockholders' Equity
(In thousands, except share amounts)

	Class A Preferred Shares		Common Shares		Additional paid-in capital	Accumulated deficit	Non-Controlling Interests	Total Stockholders' equity
	Shares	Amount	Shares	Amount				
Balance at December 31, 2020	**250,000**	**$ —**	**1,116,505**	**$ —**	**$ 75,627**	**$ (73,268)**	**$ —**	**$ 2,359**
Share based compensation	—	—	12,803	—	442	—	—	442
Issuance of common shares, net of costs	—	—	276,592	—	4,381	—	—	4,381
Cashless exercise of warrants	—	—	59	—	—	—	—	—
Net loss	—	—	—	—	—	(3,731)	—	**$ (3,731)**
Balance at December 31, 2021	**250,000**	**—**	**1,405,959**	**—**	**80,450**	**(76,999)**	**—**	**3,451**
Share based compensation	—	—	75,505	—	649	—	—	649
Common shares issuable - Founders Agreement	—	—	—	—	526	—	—	526
Issuance of common shares and pre-funded warrants at private placement, net of issuance costs	—	—	3,636,365	—	3,205	—	—	3,205
Repurchase of common stock held by InvaGen	—	—	(388,888)	—	(1,104)	—	—	(1,104)
Fortress contribution of Baergic Inc	—	—	—	—	(99)	—	—	(99)
Issuance of subsidiaries' common shares for license expenses	—	—	—	—	4	—	—	4
Exercise of warrants	—	—	44,900	—	237	—	—	237
Non-controlling interest in subsidiaries	—	—	—	—	588	—	(588)	—
Net loss attributable to non-controlling interest	—	—	—	—	—	—	(51)	(51)
Net loss attributable to common stockholders	—	—	—	—	—	(3,552)	—	(3,552)
Balance at December 31, 2022	**250,000**	**$ —**	**4,773,841**	**$ —**	**$ 84,456**	**$ (80,551)**	**$ (639)**	**$ 3,266**

The accompanying notes are an integral part of these consolidated financial statements.

AVENUE THERAPEUTICS, INC.
Consolidated Statements of Cash Flows
(In thousands)

	For the Years Ended	
	December 31, 2022	December 31, 2021
Cash flows from operating activities:		
Net loss	$ (3,603)	$ (3,731)
Adjustments to reconcile net loss to net cash used in operating activities:		
Share based compensation	649	442
Change in fair value of warrant liability	(5,580)	—
Common shares issuable - Founders Agreement	526	—
Issuance of subsidiaries' common shares for license expenses	4	—
Changes in operating assets and liabilities:		
Other receivables - related party	90	(90)
Prepaid expenses and other current assets	(30)	6
Accounts payable and accrued expenses	385	(406)
Accounts payable and accrued expenses - related party	(37)	29
Net cash and cash equivalents used in operating activities	(7,596)	(3,750)
Cash flows from financing activities:		
Proceeds from the issuance of common shares	—	5,044
Proceeds from issuance of common stock and accompanying warrants and pre-funded warrants in private placement	12,005	—
Repurchase of common stock held by InvaGen	(1,104)	—
Proceeds from exercise of warrants	148	—
Payment of offering costs	(508)	(663)
Net cash provided by financing activities	10,541	4,381
Net change in cash and cash equivalents	2,945	631
Cash and cash equivalents, beginning of period	3,763	3,132
Cash and cash equivalents, end of period	**$ 6,708**	**$ 3,763**
Supplement disclosure of non-cash information:		
Receipt of interest in Baergic from Parent	$ 99	$ —
Unpaid offering costs	$ 14	$ —

The accompanying notes are an integral part of these consolidated financial statements.

AVENUE THERAPEUTICS, INC
Notes to Consolidated Financial Statements

Note 1 — Organization, Plan of Business Operations

Avenue Therapeutics, Inc. (the "Company" or "Avenue") was incorporated in Delaware on February 9, 2015, as a wholly owned subsidiary of Fortress Biotech, Inc. ("Fortress"), to develop and market pharmaceutical products for the acute care setting in the United States. The Company is focused on developing its product candidate, an intravenous ("IV") formulation of tramadol HCI ("IV Tramadol"), for post-operative acute pain.

Baergic

On May 11, 2022, the Company entered into a stock contribution agreement (the "Contribution Agreement") with Fortress, pursuant to which Fortress agreed to transfer ownership of 100% of its shares (common and preferred) (the "Contributed Shares") in Baergic, to the Company. Under the Contribution Agreement, Fortress also agreed to assign to Avenue certain intercompany agreements existing between Fortress and Baergic, including a Founders Agreement, by and between Fortress and Baergic, dated as of March 9, 2017, and Management Services Agreement, by and between Fortress and Baergic, dated as of March 9, 2017. Consummation of the transactions contemplated by the Contribution Agreement was subject to the satisfaction of certain conditions precedent, including, inter alia: (i) the closing of an equity financing by the Company resulting in gross proceeds of at least $7.5 million, (ii) the agreement by minority Avenue shareholder InvaGen Pharmaceuticals Inc. ("InvaGen") to (A) have 100% of its shares in the Company repurchased by the Company and (B) terminate certain of the agreements into which it entered with the Company and/or Fortress in connection with InvaGen's 2019 equity investment in the Company, which would eliminate certain negative consent rights of InvaGen over the Company and restore certain rights and privileges of Fortress in the Company (all upon terms to be agreed upon with InvaGen); and (iii) the sustained listing of Avenue's common stock on The Nasdaq Capital Market.

The transaction is expected to expand Avenue's development portfolio within neuroscience. Evaluation and negotiation of the Contribution Agreement was overseen, and execution of the Contribution Agreement was approved, by special committees at the Avenue and Fortress levels, both of which exclusively comprised independent and disinterested directors of the respective companies' boards. See Note 4 below.

Reverse Stock Split

On July 25, 2022, the holders of a majority of the voting power of the capital stock of the Company executed a written consent approving a grant of discretionary authority to the board of directors of the Company (the "Board") to, without further stockholder approval, (i) effect a reverse stock split of the Company's issued and outstanding common stock within a range of between 10-for-1 and 20-for-1 (with the Board being authorized to determinate the exact ratio) (the "Reverse Stock Split") and (ii) reduce the number of the Company's authorized shares of common stock from 50,000,000 to 20,000,000 (the "Authorized Share Reduction") by filing an amendment (the "Amendment") to the Company's Third Amended and Restated Certificate of Incorporation with the Secretary of State of the State of Delaware. The written consent was signed by the holders of 9,423,429 shares of the Company's common stock and 250,000 shares of the Company's Class A Preferred Stock. Each share of common stock entitles the holder thereof to one vote on all matters submitted to stockholders and each share of Class A Preferred Stock has the voting power of 1.1 times (A) the number of outstanding shares of common stock plus (B) the whole shares of Company common stock into which the outstanding shares of Class A Preferred Stock are convertible, divided by the number of outstanding shares of Class A Preferred Stock, or 99 votes per share as of July 25, 2022. Accordingly, the holders of approximately 73% of the voting power of the Company's capital stock as of July 25, 2022 signed the written consent approving the Reverse Stock Split, the Authorized Share Reduction and the Amendment. The Board also approved the Reverse Stock Split, the Authorized Share Reduction and the Amendment.

The Reverse Stock Split was effective on September 23, 2022 upon filing of the Amendment with the Secretary of State of Delaware, which date was at least twenty (20) days from the mailing of the information statement. Under the Amendment, the number of authorized shares of Common Stock immediately after the Reverse Stock Split ("New Common Stock") was simultaneously reduced from 50,000,000 to 20,000,000 shares. All share and per share information has been retroactively adjusted to give effect to the Reverse Stock Split for all periods presented, unless otherwise indicated.

As a result of the Reverse Stock Split, every 15 shares of Common Stock outstanding immediately prior to the effectiveness of the Reverse Stock Split were combined and converted into one share of New Common Stock without any change in the par value per share. No fractional shares were issued in connection with the Reverse Stock Split. Stockholders who would otherwise be entitled to a fraction

of one share of New Common Stock as a result of the Reverse Stock Split instead received $9,580 in cash equal to such fraction multiplied by the closing sale price of Common Stock on The Nasdaq Capital Market on September 22, 2022, as adjusted for the Reverse Stock Split.

Proportionate adjustments were made to the per share exercise price and/or the number of shares issuable upon the exercise or vesting of all stock options, restricted stock and warrants outstanding at September 23, 2022, which resulted in a proportional decrease in the number of shares of the Company's common stock reserved for issuance upon exercise or vesting of such stock options, restricted stock and warrants, and, in the case of stock options and warrants, a proportional increase in the exercise price of all such stock options and warrants.

Stock Purchase and Merger Agreement

On November 12, 2018, the Company, InvaGen Pharmaceuticals Inc. ("InvaGen"), and Madison Pharmaceuticals, Inc. entered into a Stock Purchase and Merger Agreement ("SPMA"), pursuant to which the Company agreed to its sale in a two-stage transaction. In the first stage, InvaGen agreed to purchase, for $35 million, common shares representing 33.3% of the fully diluted capitalization of the Company. In the second stage, InvaGen would acquire the remaining issued and outstanding capital stock of the Company for approximately $180 million in a reverse subsidiary merger transaction (the "Merger Transaction"). The SPMA was approved by a majority of the Company's stockholders, including a majority of its non-affiliated stockholders, at its special shareholder meeting on February 6, 2019. On February 8, 2019, InvaGen acquired 388,888 shares of the Company's common stock at $90.00 per share (the "Stock Purchase Transaction") for net proceeds of $31.5 million after deducting commission fees and other offering costs, representing a 33.3% stake in the Company's capital stock on a fully diluted basis.

Consummation of the Merger Transaction was conditioned upon, among other things, U.S. Federal Drug Administration ("FDA") approval of IV Tramadol, its labeling and scheduling, and the absence of certain other restrictions in effect with respect to IV Tramadol. Pursuant to the SPMA, if FDA approval of IV Tramadol was not obtained on or before April 30, 2021, InvaGen would not be subject to the mandatory closing obligations set forth in the SPMA with respect to the Merger Transaction (but would instead retain an option to complete the Merger Transaction up until such time as the SPMA was terminated). Pursuant to the SPMA, the Company could choose to terminate the SPMA after October 31, 2021, if FDA approval of IV Tramadol had not occurred by such time. On November 1, 2021, the Company terminated the SPMA.

Even though the SPMA was terminated, InvaGen retained certain rights pursuant to the Stockholders Agreement, entered into on November 12, 2018 between the Company, InvaGen and Fortress, and other agreements entered into in connection therewith on such date. Those rights existed as long as InvaGen maintained at least 75% of the common shares acquired in the Stock Purchase Transaction and include among other things, the right to restrict the Company from certain equity issuances and changes to the Company's capital stock without obtaining InvaGen's prior written consent.

Throughout 2021, the Company communicated with InvaGen relating to InvaGen's assertions that Material Adverse Effects (as defined in the SPMA) have occurred due to the impact of the COVID-19 pandemic on potential commercialization and projected sales of IV Tramadol. Additionally, in connection with the resubmission of the Company's New Drug Application ("NDA") in February 2021, InvaGen communicated to the Company that it believes the proposed label for IV Tramadol would also constitute a Material Adverse Effect (as defined in the SPMA) on the purported basis that the proposed label under certain circumstances would make the product commercially unviable. In July 2022 we entered into a Share Repurchase Agreement with InvaGen. Upon the closing of the October 2022 public offering, InvaGen gave up all rights stated in the Stockholders Agreement and the Company repurchased the 388,888 common shares of the Company held by InvaGen. The excess of the consideration paid to InvaGen over the fair market value on the date of repurchase of $1.9 million was recognized in general and administrative expense.

Liquidity and Capital Resources

Going Concern

These consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles (GAAP) assuming the Company will continue as a going concern. The going concern assumption contemplates the realization of assets and satisfaction of liabilities in the normal course of business. However, as described below, substantial doubt about the Company's ability to continue as a going concern exists.

The Company is not yet generating revenue, has incurred substantial operating losses since its inception and expects to continue to incur significant operating losses for the foreseeable future as it executes on its product development plan and may never become profitable. As of December 31, 2022, the Company had an accumulated deficit of $80.6 million. Due to uncertainties regarding future operations of the Company for a study protocol that could form the basis for the submission of a complete response to the second Complete Response Letter for IV Tramadol, and the expansion of the Company's development portfolio within neuroscience with the consummation of the transaction with Baergic, the Company will need to secure additional funds through equity or debt offerings, or other potential sources, the timing of which is unknown at this time. The Company will require the additional funds to cover operational expenses over the next 12 months. The Company cannot be certain that additional funding will be available to it on acceptable terms, or at all. These factors individually and collectively causes substantial doubt about the Company's ability to continue as a going concern to exist within one year from the date of this report. The consolidated financial statements do not include any adjustments to the carrying amounts and classification of assets, liabilities, and reported expenses that may be necessary if the Company were unable to continue as a going concern.

Note 2 — Significant Accounting Policies

Basis of Presentation

The Company's consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("U.S. GAAP"), include all adjustments necessary for the fair presentation of the Company's financial position for the periods presented and are stated in U.S. dollars. The Company's consolidated financial statements include the accounts of the Company and the accounts of the Company's subsidiary. All intercompany balances and transactions have been eliminated.

The accompanying consolidated financial statements include the accounts of the Company's subsidiary. For consolidated entities where the Company owns less than 100% of the subsidiary, the Company records net loss attributable to non-controlling interests in its consolidated statements of operations equal to the percentage of the economic or ownership interest retained in such entities by the respective non-controlling parties. The Company continually assesses whether changes to existing relationships or future transactions may result in the consolidation or deconsolidation of partner companies.

Use of Estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of expenses during the reporting period. Actual results could differ from those estimates.

Cash and Cash Equivalents

The Company considers all short-term investments with an original maturity of three months or less when purchased to be cash equivalents. Cash and cash equivalents at December 31, 2022 and 2021 consisted of cash in institutions in the United States. The Company maintains its cash and cash equivalent balances with high-quality financial institutions and, consequently, the Company believes that such funds are currently adequately protected against credit risk. At times, portions of the Company's cash and cash equivalents may be uninsured or in deposit accounts that exceed Federal Deposit Insurance Corporation ("FDIC") insured limits. As of December 31, 2022, the Company had not experienced losses on these accounts, and management believes the Company is not exposed to significant risk on such accounts. The Company's cash equivalents and investments may comprise money market funds that are invested in U.S. Treasury obligations, corporate debt securities, U.S. Treasury obligations and government agency securities. Credit risk in these securities is reduced as a result of the Company's investment policy to limit the amount invested in any single issuer and to only invest in securities of a high credit quality. The Company has no significant off-balance sheet risk such as foreign exchange contracts, option contracts or other foreign hedging arrangements.

Other Receivables – Related Party

Other receivables consist of amounts due from Journey Medical Corporation ("Journey"), a consolidated entity under Fortress, and are recorded at the invoiced amount.

Accounts Payable and Accrued Expenses – Related Party

In the normal course of business, Fortress pays for certain expenses on behalf of the Company. Such expenses are record as accounts payable and accrued expenses – related party and are recorded at the invoiced amount and reimbursed to Fortress in the normal course of business.

Research and Development

Research and development costs are expensed as incurred. Advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made. Upfront and milestone payments due to third parties that perform research and development services on the Company's behalf will be expensed as services are rendered or when the milestone is achieved.

Research and development costs primarily consist of personnel related expenses, including salaries, benefits, travel, and other related expenses, stock-based compensation, payments made to third parties for license and milestone costs related to in-licensed products and technology, payments made to third party contract research organizations for preclinical and clinical studies, investigative sites for clinical trials, consultants, the cost of acquiring and manufacturing clinical trial materials, costs associated with regulatory filings and patents, laboratory costs and other supplies.

Costs incurred in obtaining technology licenses are charged to research and development expense if the technology licensed has not reached commercial feasibility and have no alternative future use. The licenses purchased by the Company require substantial completion of research and development, regulatory and marketing approval efforts in order to reach commercial feasibility and has no alternative future use. Accordingly, the total purchase price including any development milestone payments for the licenses acquired are reflected as research and development on our consolidated statements of operations.

Warrant Liability

We have issued freestanding warrants to purchase shares of our common stock in connection with financing activities (Warrants as described in Note 7). Our outstanding common stock warrants issued in connection with the equity financing completed in October 2022 ("October Public Offering") are classified as liabilities in the balance sheet as they contain terms for redemption of the underlying security that are outside our control. We use a Monte Carlo simulation approach to value warrants, which requires management to estimate inputs including expected volatility and expected term, and is most significantly impacted by the volatility of our common stock price. These inputs are inherently subjective and require significant analysis and judgment to develop. The fair value of all warrants is re-measured at each financial reporting date with any changes in fair value being recognized in change in fair value of warrant liabilities, a component of other income (expense), in the consolidated statements of operations and comprehensive income (loss). We will continue to re-measure the fair value of the warrant liabilities until exercise or expiration of the related warrant on October 10, 2027.

The key inputs for the Monte Carlo simulation for the year ending December 31, 2022 were as follows:

	October 11, 2022	December 31, 2022
Stock price	$ 2.84	$ 1.16
Risk-free interest rate	4.14 %	4.02 %
Expected dividend yield	—	—
Expected term in years	5.00	4.78
Expected volatility	90 %	93 %

Fair Value Measurements

The Company follows accounting guidance on fair value measurements for financial assets and liabilities measured at fair value on a recurring basis. Under the accounting guidance, fair value is defined as an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or a liability.

The accounting guidance requires fair value measurements be classified and disclosed in one of the following three categories:

Level 1: Quoted prices in active markets for identical assets or liabilities.

Level 2: Observable inputs other than Level 1 prices for similar assets or liabilities that are directly or indirectly observable in the marketplace.

Level 3: Unobservable inputs which are supported by little or no market activity and that are financial instruments whose values are determined using pricing models, discounted cash flow methodologies, or similar techniques, as well as instruments for which the determination of fair value requires significant judgment or estimation.

The fair value hierarchy also requires an entity to maximize the use of observable inputs and minimize the use of unobservable inputs when measuring fair value. Assets and liabilities measured at fair value are classified in their entirety based on the lowest level of input that is significant to the fair value measurement. The Company's assessment of the significance of a particular input to the fair value measurement in its entirety requires management to make judgments and consider factors specific to the asset or liability.

Certain of the Company's financial instruments are not measured at fair value on a recurring basis but are recorded at amounts that approximate their fair value due to their liquid or short-term nature, such as accounts payable, accrued expenses and other current liabilities.

Liabilities measured at fair value on a recurring basis as of December 31, 2022 were as follows (in thousands):

	December 31, 2022	Level 1	Level 2	Level 3
Liabilities:				
Warrant liabilities	$ 2,609	$ —	$ —	$ 2,609

The warrant liability was initially measured at $8.3 million as of October 11, 2022. For the year ended December 31, 2022, there was a $5.6 million decrease in fair value of the warrant liability primarily driven by the decrease in the Company's stock price.

Annual Stock Dividend

In September 2016, in connection with the Amended and Restated Articles of Incorporation, the Company issued 250,000 Class A Preferred shares to Fortress. The Class A Preferred shares entitled the holder to a stock dividend equal to 2.5% of the fully-diluted outstanding equity of the Company on February 16 ("The Annual Stock Dividend") to be paid on February 17 of each year. On June 13, 2018, the Company's Stockholders adopted an amendment to the Company's Third Amended and Restated Certificate of Incorporation amending the record date to December 31 and the payment date going forward to January 1 of each year. Concurrently with the execution and delivery of the SPMA, the Company, InvaGen and Fortress entered into a waiver agreement ("the Waiver Agreement"), pursuant to which, among other things, Fortress irrevocably waived its right to receive dividends of the Company's common shares under the terms of the Class A Preferred Stock and any fees, payments, reimbursements or other distributions under a certain management services agreement between the Company and Fortress and the Founders Agreement (as defined in the SPMA), for the period November 12, 2018 to the termination of InvaGen's rights under Section 4 of the Stockholders Agreement that was signed between the Company, certain stockholders of the Company, and InvaGen. As a result of the consummation of the Share Repurchase Agreement on October 31, 2022, the Waiver Agreement was terminated and the right to dividends of the Company's Common Stock was restored. The Annual Stock Dividend terminates upon conversion of the Class A Preferred shares or a Change of Control as defined in the Third Amended and Restated Certificate of Incorporation.

Pursuant to the Third Amended and Restated Certificate of Incorporation, the Company issued 231,316 shares of common stock to Fortress for the Annual Stock Dividend, representing 2.5% of the fully-diluted outstanding equity of the Company on January 1, 2023. This was shown in the consolidated statements of stockholders' equity at December 31, 2022, as part of additional paid-in capital. The Company recorded an expense of approximately $268 thousand in research and development related to these issuable shares during the year ended December 31, 2022.

Stock-Based Compensation

The Company expenses stock-based compensation to its employees, consultants and board members over the requisite service period based on the estimated grant-date fair value of the awards. Stock-based awards with graded-vesting schedules are recognized on a straight-line basis over the requisite service period for each separately vesting portion of the award. The Company accounts for forfeitures as they occur.

The assumptions used in calculating the fair value of stock-based awards represent management's best estimates and involve inherent uncertainties and the application of management's judgment.

Income Taxes

The Company accounts for income taxes under ASC 740, *Income Taxes* ("ASC 740"). ASC 740 requires the recognition of deferred tax assets and liabilities for both the expected impact of differences between the financial statement and tax basis of assets and liabilities and for the expected future tax benefit to be derived from tax loss and tax credit carry forwards. ASC 740 additionally requires a valuation allowance to be established when it is more likely than not that all or a portion of deferred tax assets will not be realized.

ASC 740 also clarifies the accounting for uncertainty in income taxes recognized in an enterprise's financial statements and prescribes a recognition threshold and measurement process for financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. For those benefits to be recognized, a tax position must be more-likely-than-not to be sustained upon examination by taxing authorities. ASC 740 also provides guidance on de-recognition, classification, interest and penalties, accounting in interim period, disclosure and transition. Based on the Company's evaluation, it has been concluded that there are no significant uncertain tax positions requiring recognition in the Company's financial statements. The 2019 through 2021 tax years are the only periods subject to examination upon filing of appropriate tax returns. The Company believes that its income tax positions and deductions would be sustained on audit and does not anticipate any adjustments that would result in a material change to its financial position.

The Company's policy for recording interest and penalties associated with audits is to record such expense as a component of income tax expense. There were no amounts accrued for penalties or interest as of or during the years ended December 31, 2022 and 2021. Management is currently unaware of any issues under review that could result in significant payments, accruals or material deviations from its position.

Non-Controlling Interests

Non-controlling interests in consolidated entities represent the component of equity in consolidated entities held by third parties. Any change in ownership of a subsidiary while the controlling financial interest is retained is accounted for as an equity transaction between the controlling and non-controlling interests.

Net Loss Per Share

Loss per share is computed by dividing net loss attributable to common stockholders by the weighted-average number of common shares outstanding, excluding unvested restricted stock and stock options and preferred shares, during the period. Dividends declared are paid and set aside among the holders of shares of common stock and Class A Preferred stock pro-rata on an as-if-converted basis.

The following table sets forth the potential common shares that could potentially dilute basic income per share in the future that were not included in the computation of diluted net loss per share because to do so would have been anti-dilutive for the periods presented:

	For the Years Ended December 31,	
	2022	2021
Unvested restricted stock units/awards	13,137	94,418
Common stock issuable	322,225	—
Warrants	4,137,916	—
Class A Preferred shares	16,666	16,666
Total potential dilutive effect	4,489,944	111,084

Recently Adopted Accounting Standards

In December 2019, the Financial Accounting Standards Board ("FASB") issued ASU No. 2019-12, *Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes,* ("ASU 2019-12") which is intended to simplify various aspects related to accounting for income taxes. ASU 2019-12 removes certain exceptions to the general principles in Topic 740 and also clarifies and amends existing guidance to improve consistent application. This guidance is effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2020, with early adoption permitted. The Company adopted ASU 2019-12 on January 1, 2021 and its adoption did not have a material impact on the Company's consolidated financial statements and related disclosures.

Note 3 — License/Supplier Agreements

Effective as of February 17, 2015, Fortress transferred the Revogenex license and all other rights and obligations under the License Agreement to the Company, pursuant to the terms of the Founders Agreement. In connection with the terms of the License Agreement, Fortress purchased an exclusive license to IV Tramadol for the U.S. market from Revogenex, a privately held company in Dublin, Ireland. Fortress made an upfront payment of $2.0 million to Revogenex upon execution of the exclusive license, and on June 17, 2015, Fortress paid an additional $1.0 million to Revogenex after receiving all the assets specified in the agreement. In December 2019, $1.0 million became due to Revogenex in accordance with the Company's submission of its NDA. In addition, under the terms of the agreement, Revogenex is eligible to receive an additional milestone payment totaling $3.0 million upon the approval of IV Tramadol from the FDA as well as royalty payments on net sales of the product ranging in the high single digits to low double digits.

On October 29, 2018, the Company and Zaklady Farmaceutyczne Polpharma ("Polpharma") extended the term of their exclusive supply agreement for drug product of IV Tramadol to eight years from the date of the launch of the product. In addition, under the terms of the amended agreement, Polpharma is eligible to receive a milestone payment totaling $2.0 million upon the approval of IV Tramadol from the FDA, as well as a low single digit royalty on net sales of the product for five years after launch.

Baergic Licenses

In December 2019, Baergic entered into two license agreements: (i) a license agreement (the "AZ License") with AstraZeneca AB ("AZ") to acquire an exclusive license to patent and related intellectual property rights pertaining to their proprietary compound Gamma-aminobutyric acid receptor A alpha 2 & 3 (GABAA α2,3) positive allosteric modulators; and (ii) a license agreement (the "CCHMC License") with Cincinnati Children's Hospital Medical Center ("CCHMC") to acquire patent and related intellectual property rights pertaining to a GABA inhibitor program for neurological disorders. Baergic paid an upfront fee of $3.0 million to AZ and $0.2 million to CCHMC, as well as issued common shares of Baergic of approximately 20% and 5% of Baergic to each at the time of the license agreement, respectively.

Development milestones totaling approximately $81.5 million in the aggregate are due upon achievement of each milestone. Commercial and sales-based milestone payments totaling approximately $151 million are due upon achievement of each milestone, as well as royalty payments in the low to high single digits on any future aggregate, annual, worldwide net sales.

Note 4 — Related Party Agreements

Founders Agreement and Management Services Agreement with Fortress

Fortress entered into a Founders Agreement with Avenue in February 2015 (as amended, the "Fortress-Avenue Founders Agreement"), pursuant to which Fortress assigned to Avenue all of its rights and interest under Fortress's license agreement with Revogenex for IV Tramadol (the "License Agreement"). As partial consideration for the Fortress-Avenue Founders Agreement, Avenue assumed $3.0 million in debt that Fortress had accumulated for expenses and costs of forming Avenue and obtaining the IV Tramadol license. This debt was repaid to Fortress in 2017. As additional consideration for the transfer of rights under the original Fortress-Avenue Founders Agreement, Avenue also agreed to: (i) issue annually to Fortress, on the anniversary date of the Fortress-Avenue Founders Agreement, shares of common stock equal to two and one half percent (2.5%) of the fully-diluted outstanding equity of Avenue; (ii) pay an equity fee in shares of Avenue common stock, payable within five (5) business days of the closing of any equity or debt financing for Avenue or any of its respective subsidiaries that occurs after the effective date of the Founders Agreement and ending on the date when Fortress no longer has majority voting control in Avenue's voting equity, equal to two and one half percent (2.5%) of the gross amount of any such equity or debt financing; and (iii) pay a cash fee equal to four and one half percent (4.5%) of Avenue's annual net sales, payable on an annual basis, within ninety (90) days of the end of each calendar year. In the event of a change in control (as it is defined in the Founders Agreement), Fortress will be paid a one-time change in control fee equal to five (5x) times the product of (i) net sales for the twelve (12) months immediately preceding the change in control and (ii) four and one-half percent (4.5%).

On September 13, 2016, the Company amended the Fortress-Avenue Founders Agreement to remove the Annual Equity Fee (that feature remained in substance and became issuable to the holders of Avenue's Class A Preferred Stock, all of which is currently held by Fortress) and to add a term of 15 years, which upon expiration automatically renews for successive one-year periods unless terminated by Fortress or a Change in Control occurs. Concurrently with effecting such amendment of the Fortress-Avenue Founders Agreement, the Company entered into an Exchange Agreement whereby the Company exchanged Fortress' 155,555 Class A common shares for approximately 166,027 common shares and 250,000 Class A Preferred shares (see Note 7).

Effective as of February 17, 2015, Fortress entered into a Management Services Agreement (the "Fortress-Avenue MSA") with Avenue pursuant to which Fortress provides advisory and consulting services to Avenue pursuant to the terms thereof. The Fortress-Avenue MSA contained an initial five-year term and shall be automatically extended for additional five-year periods unless Fortress or the Company provides written notice of its desire not to automatically extend the term of the MSA at least 90 days prior to the applicable expiration date. Services provided under the Fortress-Avenue MSA may include, without limitation, (i) advice and assistance concerning any and all aspects of Avenue's operations, clinical trials, financial planning and strategic transactions and financings and (ii) conducting relations on behalf of Avenue with accountants, attorneys, financial advisors and other professionals (collectively, the "Services"). Avenue is obligated to utilize clinical research services, medical education, communication and marketing services and investor relations/public relation services of companies or individuals designated by Fortress, provided those services are offered at market prices. However, Avenue is not obligated to take or act upon any advice rendered from Fortress, and Fortress shall not be liable for any of Avenue's actions or inactions based upon their advice. Fortress and its affiliates, including all members of Avenue's Board of Directors, have been contractually exempt from fiduciary duties to Avenue relating to corporate opportunities. In consideration for the Services, Avenue will pay Fortress an annual consulting fee of $0.5 million (the "Annual Consulting Fee"), payable in advance in equal quarterly installments on the first business day of each calendar quarter in each year, provided, however, that such Annual Consulting Fee shall be increased to $1.0 million for each calendar year in which Avenue has net assets in excess of $100.0 million at the beginning of the calendar year. Effective beginning on November 12, 2018, eligibility to receive such fees was waived pursuant to a Waiver Agreement signed between Avenue, Fortress and InvaGen. The Fortress-Avenue MSA fee was reinstated upon the closing of the October 2022 public offering.

Founders Agreement and Management Services Agreement with Baergic

Pursuant to the Share Contribution Agreement between Avenue and Fortress, the Founders Agreement and Management Services Agreement that had previously been existing between Fortress and Baergic were assigned to Avenue, such that they now exist between Avenue and Baergic; those agreements are referred to herein as the Avenue-Baergic Founders Agreement and the Avenue-Baergic MSA, as applicable. The Annual Stock Dividend payable to the Company is 2.5% of common stock calculated as a percentage of fully diluted outstanding capital and became effective as of November 8, 2022. For the year ended December 31, 2022, Baergic recorded an Annual Stock Dividend of $10.5 thousand to Avenue on December 31, 2022, which was paid in shares on January 1, 2023.

The Avenue-Baergic Founders Agreement has an effective date of March 9, 2017, and a term of 15 years, which upon expiration automatically renews for successive one-year periods unless terminated by Avenue and Baergic or a Change in Control (as defined in the Avenue-Baergic Founders Agreement) occurs.

As additional consideration under the Avenue-Baergic Founders Agreement, Baergic will also: (i) pay an equity fee in shares of common stock, payable within five (5) business days of the closing of any equity or debt financing for Baergic that occurs after the effective date of the Avenue-Baergic Founders Agreement and ending on the date when Avenue no longer has majority voting control in the Baergic's voting equity, equal to two and one-half (2.5%) of the gross amount of any such equity or debt financing; and (ii) pay a cash fee equal to four and one-half percent (4.5%) of the Baergic's annual net sales, payable on an annual basis, within ninety (90) days of the end of each calendar year. In the event of a Change in Control, Baergic will pay a one-time change in control fee equal to five (5x) times the product of (A) net sales for the twelve (12) months immediately preceding the change in control and (B) four and one-half percent (4.5%).

The Avenue-Baergic MSA has an effective date of March 9, 2017, pursuant to which Avenue renders management, advisory and consulting services to the Company. The MSA has an initial term of five years and is automatically renewed for successive five-year terms unless terminated in accordance with its provisions. Services provided under the MSA may include, without limitation, (i) advice and assistance concerning any and all aspects of the Baergic's operations, clinical trials, financial planning and strategic transactions and financings and (ii) conducting relations on behalf of the Baergic with accountants, attorneys, financial advisors and other professionals (collectively, the "Avenue Services"). Baergic is obligated to utilize clinical research services, medical education, communication and marketing services and investor relations/public relation services of companies or individuals designated by Avenue, provided those services are offered at market prices. However, Baergic is not obligated to take or act upon any advice rendered from Avenue and Avenue shall not be liable for any of its actions or inactions based upon their advice. Pursuant to the Avenue-Baergic MSA and Baergic's Certificate of Incorporation, Avenue and its affiliates, including all members of Baergic's Board of Directors, will have no fiduciary or other duty to communicate or present any corporate opportunities to Baergic or to refrain from engaging in business that is similar to that of Baergic. In consideration for the Avenue Services, Baergic will pay Avenue an annual consulting fee of $0.5 million (the "Avenue-Baergic Annual Consulting Fee"), payable in advance in equal quarterly installments on the first business day of each calendar quarter in each year, provided, however, that such Avenue-Baergic Annual Consulting Fee shall be increased to $1.0 million for each calendar year in which Baergic has net assets in excess of $100 million at the beginning of the calendar year.

Secondment Agreement with Journey

Effective June 1, 2021, the Company, InvaGen, Fortress and Journey entered into a secondment agreement for a certain Avenue employee to be seconded to Journey. During the secondment, Journey had the authority to supervise the Avenue employee and will reimburse the Company for the employee's salary and salary-related costs. The term of this agreement lasted until the employee's services were needed again by the Company which was December 1, 2021. The amounts reimbursable to Avenue were zero and $0.2 million for the years ended December 31, 2022 and December 31, 2021, respectively. The amounts were recorded as a reduction in research and development expenses on the Company's consolidated statements of operations. The amount due to the Company as of December 31, 2021 that is related to this secondment agreement is $90,000 and is included in "Other receivables – related party" on the Company's consolidated balance sheets.

Acquisition of Baergic

On May 11, 2022, the Company entered into the Contribution Agreement with Fortress related to the Company's acquisition of Baergic, on the terms and subject to the satisfaction of conditions described above in Note 1 – Organization, Plan of Business Operations. Evaluation and negotiation of the Contribution Agreement was overseen, and execution of the Contribution Agreement was approved, by special committees at the Avenue and Fortress levels, both of which exclusively comprised independent and disinterested directors of the respective companies' boards. The Company believes that the terms of the Contribution Agreement is at least as favorable as the terms that the Company would have been able to obtain with a disinterested party.

The transaction was accounted for as an asset acquisition between entities under common control. As such, the transaction was recorded at carryover basis, with all assets, liabilities and non-controlling interests measured at their historical carrying values. The consolidated financial statements of the Company include the consolidated results of operations for Avenue and Baergic since the acquisition date on November 8, 2022.

Note 5 — Accounts Payable and Accrued Expenses

Accounts payable, accrued expenses and other liabilities consisted of the following (in thousands):

	As of December 31,	
	2022	2021
Accounts payable	$ 129	$ 304
Accrued employee compensation	199	24
InvaGen contingent fee	208	—
Accrued contracted services and other	413	123
Accounts payable and accrued expenses	$ 949	$ 451

Note 6 — Commitments and Contingencies

Leases

The Company is not a party to any leases for office space or equipment.

Litigation

The Company recognizes a liability for a contingency when it is probable that liability has been incurred and when the amount of loss can be reasonably estimated. When a range of probable loss can be estimated, the Company accrues the most likely amount of such loss, and if such amount is not determinable, then the Company accrues the minimum of the range of probable loss. As of December 31, 2022 and 2021, there was no litigation against the Company.

Note 7 — Stockholders' Equity

Class A Preferred Shares

On September 13, 2016, 2,000,000 shares of Preferred Stock were authorized, of which 250,000 have been designated as Class A Preferred Stock and the remainder are undesignated preferred stock. The Class A Preferred Stock, with a par value of $0.0001 per share, is identical to undesignated Common Stock other than as to voting rights, conversion rights, and the Annual Stock Dividend right (as described below). The undesignated Preferred Stock may be issued from time to time in one or more series. The Company's Board of Directors is authorized to determine or alter the dividend rights, dividend rate, conversion rights, voting rights, rights and terms of redemption (including sinking fund provisions, if any), the redemption price or prices, the liquidation preferences and other designations, powers, preferences and relative, participating, optional or other special rights, if any, and the qualifications, limitations and restrictions granted to or imposed upon any wholly unissued series of Preferred Stock, and to fix the number of shares of any series of Preferred Stock (but not below the number of shares of any such series then outstanding).

On any matter presented to the stockholders of the Company for their action or consideration at any meeting of stockholders of the Company (or by written consent of stockholders in lieu of meeting), each holder of outstanding shares of Class A Preferred Stock shall be entitled to cast for each share of Class A Preferred Stock held by such holder as of the record date for determining stockholders entitled to vote on such matter, the number of votes that is equal to one and one-tenth (1.1) times a fraction, the numerator of which is the sum of (A) the number of shares of outstanding Common Stock and (B) the whole shares of Common Stock in to which the shares of outstanding Class A Preferred Stock are convertible, and the denominator of which is number of shares of outstanding Class A Preferred Stock (the "Class A Preferred Stock Ratio"). Thus, the Class A Preferred Stock will at all times constitute a voting majority.

Each share of Class A Preferred Stock is convertible, at the option of the holder, into one fully paid and nonassessable share of Common Stock (the "Conversion Ratio"), subject to certain adjustments. If the Company, at any time effects a subdivision or combination of the outstanding Common Stock (by any stock split, stock dividend, recapitalization, reverse stock split or otherwise), the applicable Conversion Ratio in effect immediately before that subdivision is proportionately decreased or increased, as applicable, so that the number of shares of Common Stock issuable on conversion of each share of Class A Preferred Stock shall be increased or decreased, a applicable, in proportion to such increase or decrease in the aggregate number of shares of Common Stock outstanding. Additionally, if any reorganization, recapitalization, reclassification, consolidation or merger involving the Company occurs in which the Common Stock (but not the Class A Preferred Stock) is converted into or exchanged for securities, cash or other property, then each share of Class A Preferred Stock becomes convertible into the kind and amount of securities, cash or other property which a holder of the number of shares of Common Stock of the Company issuable upon conversion of one share of the Class A Preferred Stock immediately prior to such reorganization, recapitalization, reclassification, consolidation or merger would have been entitled to receive pursuant to such transaction. Pursuant to the reverse stock split by the Company in September 2022, the Class A Preferred Stock has a Conversion Ratio of 15 Class A Preferred to one share of Common Stock.

Common Stock

As of December 31, 2022, the Company's authorized capital stock consists of 20,000,000 shares of common stock, with $0.0001 par value (see Note 1).

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

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

In November 2021, the Company, pursuant to an underwritten public offering, sold 149,252 shares of its common stock at a price of $20.10 per share for gross proceeds of approximately $3.0 million. After deducting underwriting discounts and commissions and other expenses, net proceeds from this underwritten public offering were $2.6 million.

In December 2021, the Company, pursuant to an underwritten public offering, sold 127,340 shares of its common stock at a price of $16.05 per share for gross proceeds of approximately $2.0 million. In addition, the Company granted the underwriters a 45-day option to purchase additional shares of common stock, representing up to 15% of the number of the shares, solely to cover over-allotments. This 45-day purchase option was not exercised. After deducting underwriting discounts and commissions and other expenses, net proceeds from this underwritten public offering were $1.8 million.

Pursuant to the October 2022 Offering, the Company sold 2,652,065 units ("Units") and 984,300 pre-funded units ("Pre-funded Units"). Each Unit consisted of one share (a "Share") of the Company's common stock, par value $0.0001 per share ("Common Stock"), and one warrant to purchase one share of Common Stock (each, a "Warrant" and, collectively, the "Warrants"), and each Pre-funded Unit consisted of one pre-funded warrant to purchase one share of Common Stock (each, a "Pre-funded Warrant" and collectively, the "Pre-funded Warrants") and one Warrant. The Units were sold at a price of $3.30 per Unit, and the Pre-Funded Units were sold at a price of $3.2999 ($3.30 less $0.0001, the exercise price of the Pre-funded Warrants).

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

The Company received net proceeds from the Offering of $10.3 million, after deducting underwriting discounts and commissions and estimated offering expenses payable by the Company.

Pursuant to the Founders Agreement, the Company issued 90,909 shares of common stock to Fortress related to the October 2022 offering, which is equivalent to 2.5% of the gross amount of the offering. The Company recorded the expense of $0.3 million in research and development on the record date and issued the shares on January 1, 2023.

Equity Incentive Plan

The Company has in effect the 2015 Incentive Plan ("2015 Incentive Plan'). The 2015 Incentive Plan was adopted in January 2015 by our stockholders and an amendment to the plan to increase the number of authorized shares issuable to 266,666 shares was approved by our stockholders in December 2021. Under the 2015 Incentive Plan, the compensation committee of the Company's board of directors is authorized to grant stock-based awards to directors, officers, employees and consultants. The plan authorizes grants to issue up to 266,666 shares of authorized but unissued common stock and expires 10 years from adoption and limits the term of each option to no more than 10 years from the date of grant.

Total shares available for the issuance of stock-based awards under the Company's 2015 Incentive Plan was 122,489 shares at December 31, 2022.

Restricted Stock Units and Restricted Stock Awards

The following table summarizes restricted stock unit and award activity for the year ended December 31, 2022:

	Number of Units and Awards	Weighted Average Grant Date Fair Value
Unvested balance at December 31, 2020	75,993	$ 89.40
Granted	55,977	13.95
Forfeited	(29,174)	119.70
Vested	(8,378)	74.55
Unvested balance at December 31, 2021	94,418	$ 56.25
Forfeited	(666)	13.95
Vested	(80,615)	40.83
Unvested balance at December 31, 2022	13,137	$ 12.17

For the years ended December 31, 2022, and 2021 stock-based compensation expenses associated with the amortization of restricted stock units and restricted stock awards for employees and non-employees were approximately $0.6 million and $0.4 million, respectively.

For the years ended December 31, 2022, and 2021, the weighted average grant date fair value of restricted stock units and awards granted was zero and $13.95, respectively. For the years ended December 31, 2022, and 2021, the weighted average grant date fair value of restricted stock units and awards forfeited was $13.95 and $119.70, respectively. The total fair value of restricted stock units and awards that vested during the years ended December 31, 2022, and 2021 was $3.3 million and $0.6 million, respectively.

At December 31, 2022, the Company had unrecognized stock-based compensation expense related to restricted stock units and restricted stock awards of $0.1 million, which is expected to be recognized over the remaining weighted-average vesting period of 1.96 years. This amount does not include, as of December 31, 2022, 3,333 shares of restricted stock outstanding which are performance-based and vest upon achievement of certain corporate milestones. The expense is recognized over the vesting period of the award. Stock-based compensation for awards containing performance conditions will be measured as of the grant date and recorded if and when it is probable that the performance condition will be achieved.

Stock Warrants

The following table summarizes the warrant activity for the years ended December 31, 2021 and 2022:

	Warrants	Weighted Average Exercise Price	Aggregate Intrinsic Value (in thousands)
Outstanding, December 31, 2020	1,056	$ 9.4231	$ 84
Exercised	(59)	0.0015	—
Outstanding, December 31, 2021	997	$ 9.9807	$ 11
Granted	5,166,119	2.6713	—
Exercised	(1,029,200)	0.1441	—
Outstanding, December 31, 2022	4,137,916	$ 3.3016	$ 1

Upon the exercise of warrants, the Company will issue new shares of its common stock.

Public Offering Warrant Liabilities

In October 2022, the Company sold 2,652,065 units ("Units") and 984,300 pre-funded units ("Pre-funded Units"). Each Unit consisted of one share (a "Share") of the Company's common stock ("Common Stock"), and one warrant to purchase one share of Common Stock (each, a "Warrant" and, collectively, the "Warrants"), and each Pre-funded Unit consisted of one pre-funded warrant to purchase one share of Common Stock (each, a "Pre-funded Warrant" and collectively, the "Pre-funded Warrants") and one Warrant. The Units were sold at a price of $3.30 per Unit, and the Pre-Funded Units were sold at a price of $3.2999 ($3.30 less $0.0001, the exercise price of the Pre-funded Warrants). Net proceeds from the offering were $10.3 million after deducting underwriting discounts and commissions and other transaction costs.

We account for warrants as either equity-classified or liability-classified instruments based on an assessment of the warrant's specific terms and applicable authoritative guidance in ASC 480 and ASC 815. The assessment considers whether the warrants are freestanding financial instruments pursuant to ASC 480, meet the definition of a liability pursuant to ASC 480, and whether the warrants meet all of the requirements for equity classification under ASC 815, including whether the warrants are indexed to the Company's own common stock, among other conditions for equity classification. This assessment, which requires the use of professional judgment, is conducted at the time of warrant issuance and as of each subsequent quarterly period end date while the warrants are outstanding.

For issued or modified warrants that meet all of the criteria for equity classification, the warrants are required to be recorded as a component of additional paid-in capital at the time of issuance. For issued or modified warrants that do not meet all the criteria for equity classification, the warrants are required to be recorded at their initial fair value on the date of issuance, and each consolidated balance sheet date thereafter. Changes in the estimated fair value of the warrants are recognized as a gain or loss on the consolidated statements of operations. The fair value of the warrants was estimated using a Monte Carlo simulation approach (see Note 2).

The Company deemed the October 2022 Warrants to be classified as liabilities on the consolidated balance sheet as they contain terms for redemption of the underlying security that are outside of the Company's control. The Warrants were recorded at the time of closing at a fair value of $8.3 million, determined by using the Monte Carlo simulation approach.

The Company revalued the October 2022 Warrants at December 31, 2022 using the Monte Carlo simulation approach. This resulted in a decrease in common stock warrant liability of $5.6 million, with an offsetting gain recorded to change in fair value of common stock warrant liabilities in the consolidated statements of operations.

Note 8 — Income Taxes

The Company has accumulated net losses since inception and has not recorded an income tax provision or benefit during the years ended December 31, 2022 and 2021.

A reconciliation of the statutory U.S. federal rate to the Company's effective tax rate is as follows:

	For the years ended December 31,	
	2022	2021
Statutory federal income tax rate	21 %	21 %
State taxes, net of federal tax benefit	10 %	13 %
State rate change	(1)%	0 %
Stock-based compensation	(22)%	(11)%
Other	3 %	0 %
Credits	4 %	0 %
None-deductible items	(12)%	0 %
Section 162(m) disallowance	(3)%	0 %
Change in fair value of warrant liability	48 %	0 %
Change in valuation allowance	(49)%	(23)%
Income taxes provision (benefit)	0 %	0 %

The components of the net deferred tax asset as of December 31, 2022 and 2021 are the following (in thousands):

	As of December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 25,660	$ 23,719
Stock compensation and other	42	293
In process research and development	1,603	1,162
Accruals and reserves	64	6
Business interest expense disallowance	122	—
Section 174 capitalization	622	—
Tax credits	2,859	2,640
Total deferred tax assets	30,972	27,820
Less valuation allowance	(30,972)	(27,820)
Deferred tax assets, net of valuation allowance	$ —	$ —

The Company has determined, based upon available evidence, that it is more likely than not that the net deferred tax asset will not be realized and, accordingly, has provided a full valuation allowance against it. A valuation allowance of approximately $31.0 million and $27.8 million was recorded as of December 31, 2022 and 2021, respectively.

As of December 31, 2022, the Company had federal and state net operating loss carryforwards of approximately $78.3 million and $139.7 million, respectively. Approximately $63.8 million of the federal net operating loss carryforwards and $1.9 million of the state net operating loss carryforwards can be carried forward indefinitely. The remaining $14.5 million of federal and $137.8 million of state net operating loss carryforwards will begin to expire, if not utilized, by 2034 and 2034, respectively. The Company has $2.9 million of research and development credit carryforwards, which will begin to expire, if not utilized, in 2034. Utilization of the net operating loss and credit carryforwards may be subject to an annual limitation due to the ownership change limitations provided by Section 382 of the Internal Revenue Code. The Company has not performed a Section 382 analysis as of December 31, 2022.

There are no significant matters determined to be unrecognized tax benefits taken or expected to be taken in a tax return, in accordance with ASC 740, which clarifies the accounting for uncertainty in income taxes recognized in the consolidated financial statements, that have been recorded on the Company's consolidated financial statements for the periods ended December 31, 2022 and 2021. The Company does not anticipate a material change to unrecognized tax benefits in the next twelve months.

Additionally, ASC 740 provides guidance on the recognition of interest and penalties related to income taxes. There were no interest or penalties related to income taxes that have been accrued or recognized as of and for the periods ended December 31, 2022 and 2021.

The federal and state tax returns for the years ended December 31, 2019, 2020, and 2021 are currently open for examination under applicable federal and state income tax statues of limitations. The company is not currently under examination.

Note 9 — Subsequent Events

January 2023 Registered Offering and Private Placement

On January 27, 2023, the Company entered into a Registered Direct and Private Placement agreement with a single institutional investor for the sale of 448,000 shares of common stock at a price per share of $1.55, and pre-funded warrants to purchase 1,492,299 shares of common stock, at a price per pre-funded warrant of $1.549. The pre-funded warrants have an exercise price of $0.001 per share and became exercisable upon issuance and remain exercisable until exercised in full. In a concurrent Private Placement, the Company also agreed to issue to the same investor warrants to purchase 1,940,299 shares of common stock ("PIPE Warrants"). The PIPE Warrants had an offering price of $0.125 per PIPE Warrant to purchase one share of common stock. The PIPE Warrants have an exercise price of $1.55 per share and are exercisable six months after issuance and will expire three years from the date on which the PIPE Warrants become exercisable. The Company received gross proceeds of $3.25 million total from both offerings.

AnnJi License Agreement

On February 28, 2023, the Company entered into a license agreement with AnnJi Pharmaceutical Co. Ltd., whereby the Company obtained an exclusive license (the "License Agreement") 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 U.S. for the treatment of spinal and bulbar muscular atrophy ("SBMA"), also known as Kennedy's Disease. Under the License Agreement, in exchange for exclusive rights to the intellectual property underlying the AJ201 product candidate, the Company will pay an initial cash license fee of $3.0 million, of which $2.0 million is payable within 60 days and $1 million is payable within 180 days after the effective date of the License Agreement.

The license provided under the License Agreement is exclusive as to all oral forms of AJ201 for use in all indications (other than androgenetic alopecia and Alzheimer's disease) in the United States, Canada, the European Union, the United Kingdom and Israel. The License Agreement also contains customary representations and warranties and provisions related to confidentiality, diligence, indemnification and intellectual property protection. The Company will initially be obligated to obtain both clinical and commercial supply of AJ201 exclusively through AnnJi.

The Company is also obligated to issue shares of its common stock under the Subscription Agreement and make additional payments over the course of the License Agreement including: reimbursement payments of up to $10.8 million in connection with the product's Phase 1b/2a clinical trial, up to $14.5 million in connection with certain development milestones pertaining to the first indication in the U.S., up to $27.5 million in connection with certain drug development milestones pertaining to additional indications and development outside the U.S., up to $165 million upon the achievement of certain net sales milestones ranging from $75 million to $750 million in annual net sales, and royalty payments based on a percentage of net sales ranging from mid-single digits (on annual net sales at or below $50 million) to the low double digits (on annual net sales equal to or greater than $300 million), which are subject to potential diminution in certain circumstances.

In connection with the signing of the License Agreement, the Company will issue 831,618 shares of its common stock to AnnJi ("First Tranche Shares") and then will issue an additional 276,652 shares of common stock upon enrollment of the eighth patient in the ongoing Phase 1b/2a SBMA clinical trial ("Second Tranche Shares"). The Company and AnnJi entered into a subscription agreement, dated as of February 28, 2023, that provides for the issuance of First Tranche Shares, which contains customary representations and warranties of the Company and AnnJi, respectively, and is subject to customary closing conditions. The Company and AnnJi will enter into a subsequent subscription agreement, in substantially the same form as the Subscription Agreement, with respect to the issuance of the Second Tranche Shares. Also in connection with execution of the License Agreement, the Company entered into a registration rights agreement with AnnJi. Pursuant to the Registration Rights Agreement, the Company will be required to file, on or prior to August 28, 2023, a registration statement with the U.S. Securities and Exchange Commission to register the resale of the Consideration Shares.

SIGNATURES

Pursuant to the requirements of Section 12 of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Avenue Therapeutics, Inc.

By: /s/ Alexandra MacLean, M.D.
Name: Alexandra MacLean, M.D.
Title: Chief Executive Officer and Director
March 31, 2023

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Alexandra MacLean, M.D. Alexandra MacLean, M.D.	Chief Executive Officer and Director (Principal Executive Officer)	March 31, 2023
/s/ David Jin David Jin	Interim Chief Financial Officer and Chief Operating Officer (Principal Financial and Accounting Officer)	March 31, 2023
/s/ Jay Kranzler, M.D., Ph.D. Jay Kranzler, M.D., Ph.D.	Chairman of the Board	March 31, 2023
/s/ Faith Charles Faith Charles	Director	March 31, 2023
/s/ Neil Herskowitz Neil Herskowitz	Director	March 31, 2023
/s/ Curtis Oltmans Curtis Oltmans	Director	March 31, 2023
/s/ Lindsay A. Rosenwald, M.D. Lindsay A. Rosenwald, M.D.	Director	March 31, 2023

Exhibit 4.3

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934
DESCRIPTION OF CAPITAL STOCK

Authorized Capital Stock

Our authorized capital stock consists of 75,000,000 shares of common stock, with $0.0001 par value ("**Common Stock**"), 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.

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.

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.

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.

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.

Preferred Stock

Class A Preferred Stock

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

the number of shares of outstanding Class A Preferred Stock. Thus, the Class A Preferred Stock will at all times constitute a voting majority.

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

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

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

Undesignated Preferred Stock

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

Warrants

We have issued, and may in the future issue additional, warrants to purchase shares of our Common Stock and/or preferred stock in one or more series together with other securities or separately.

Cash Warrants Issued in October 2022

Exercisability

The warrants issued on October 11, 2022 (the "**2022 Warrants**") became exercisable upon issuance and at any time up to the date that is five years after their original issuance. The 2022 Warrants became upon issuance, 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 2022 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 2022 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 2022 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 2022 Warrant. No fractional shares of Common Stock will be issued in connection with the exercise of a 2022 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 2022 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 2022 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 2022 Warrants was originally $3.30, but has since been reduced 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.

Dilutive Issuance Adjustments

If, while the 2022 Warrants are outstanding, we engage in any transaction involving the issue or sale of our shares of Common Stock or equivalent securities at an effective price per share less than the exercise price of the 2022 Warrants then in effect (such lower price, the "**Base Share Price**"), the exercise price of the 2022 Warrants shall be reduced to equal the Base Share Price. There shall only be one such adjustment to the exercise price, if any, while the 2022 Warrants are outstanding. This adjustment occurred effective as of the close of business on January 27, 2023.

Transferability

Subject to applicable laws, the 2022 Warrants may be offered for sale, sold, transferred or assigned without our consent.

Exchange Listing

The 2022 Warrants are not listed on any securities exchange or nationally recognized trading system.

Warrant Agent

The 2022 Warrants were issued in registered form under a warrant agency agreement between VStock Transfer, LLC, as warrant agent, and us. The 2022 Warrants were initially be represented only by one or more global warrants deposited with the warrant agent, as custodian on behalf of The Depository Trust Company (DTC) and registered in the name of Cede & Co., a nominee of DTC, or as otherwise directed by DTC.

Fundamental Transactions

In the event of a fundamental transaction, as described in the 2022 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 2022 Warrants will be entitled to receive upon exercise of the 2022 Warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the 2022 Warrants immediately prior to such fundamental transaction.

Rights as a Stockholder

Except as otherwise provided in the 2022 Warrants or by virtue of such holder's ownership of shares of our Common Stock, the holder of a 2022 Warrant does not have the rights or privileges of a holder of our Common Stock, including any voting rights, until the holder exercises the 2022 Warrant.

Governing Law

The 2022 Warrants and the warrant agency agreement are governed by New York law.

Pre-funded Warrants Issued in October 2022

Exercisability

The pre-funded warrants issued on October 11, 2022 (the "**2022 Pre-funded Warrants**") became exercisable upon issuance and may be exercised at any time until the 2022 Pre-funded Warrants are exercised in full. The 2022 Pre-funded Warrants will be exercisable, at the option of each holder, in whole or in part by delivering to us a duly executed exercise notice and, at any time a registration statement registering the offer and sale of the shares of Common Stock underlying the 2022 Pre-funded Warrants under the Securities Act is effective and available for the issuance of such shares, or an exemption from registration under the Securities Act is available for the issuance of such shares, by payment in full 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 2022 Pre-funded 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 2022 Pre-funded Warrants through a cashless exercise, in which case the holder would receive upon such exercise the net number of shares of Common Stock determined according to the formula set forth in the 2022 Pre-funded Warrant. No fractional shares of Common Stock will be issued in connection with the exercise of a 2022 Pre-funded 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 2022 Pre-funded Warrants 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 2022 Pre-funded Warrants. However, any holder may increase or decrease such percentage to any other percentage not in excess of 9.99%, provided that any increase in such percentage shall not be effective until 61 days following notice from the holder to us.

Exercise Price

The exercise price per whole share of Common Stock purchasable upon exercise of the 2022 Pre-funded Warrants is $0.0001. 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 2022 Pre-funded Warrants may be offered for sale, sold, transferred or assigned without our consent.

Exchange Listing

The 2022 Pre-funded Warrants are not listed on any securities exchange or nationally recognized trading system.

Warrant Agent

The 2022 Pre-funded Warrants were issued in registered form under a warrant agency agreement between VStock Transfer, LLC, as warrant agent, and us. The 2022 Pre-funded Warrants were initially be represented only by one or more global warrants deposited with the warrant agent, as custodian on behalf of The Depository Trust Company (DTC) and registered in the name of Cede & Co., a nominee of DTC, or as otherwise directed by DTC.

Fundamental Transactions

In the event of a fundamental transaction, as described in the 2022 Pre-funded Warrants and generally including any reorganization, recapitalization or reclassification of our Common Stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of more than 50% of our outstanding Common Stock, or any person or group becoming the beneficial owner of 50% of the voting power represented by our outstanding Common Stock, the holders of the 2022 Pre-funded Warrants will be entitled to receive upon exercise of the 2022 Pre-funded Warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the 2022 Pre-funded Warrants immediately prior to such fundamental transaction.

Rights as a Stockholder

Except as otherwise provided in the 2022 Pre-funded Warrants or by virtue of such holder's ownership of shares of our Common Stock, the holder of a 2022 Pre-funded Warrant does not have the rights or privileges of a holder of our Common Stock, including any voting rights, until the holder exercises the 2022 Pre-funded Warrant.

Governing Law

The 2022 Pre-funded Warrants and the warrant agency agreement are governed by New York law.

Pre-funded Warrants Issued in January 2023

Exercisability

The pre-funded warrants issued on January 31, 2023 (the "**2023 Pre-funded Warrants**") became exercisable upon issuance and may be exercised at any time until the 2023 Pre-funded Warrants are exercised in full. The 2023 Pre-funded Warrants will be exercisable, at the option of each holder, in whole or in part by delivering to us a duly executed exercise notice and, at any time a registration statement registering the offer and sale of the shares of Common Stock underlying the 2023 Pre-funded Warrants under the Securities Act is effective and available for the issuance of such shares, or an exemption from registration under the Securities Act is available for the issuance of such shares, by payment in full of the exercise price of $0.001 per share in immediately available funds for the number of shares of Common Stock purchased upon such exercise. Alternatively, the holder may elect to exercise the 2023 Pre-funded Warrants through a cashless exercise, in which case the holder would receive upon such exercise the net number of shares of Common Stock determined according to the formula set forth in the Pre-funded Warrant. No fractional shares of Common Stock will be issued in connection with the exercise of a Pre-funded Warrant. In lieu of fractional shares, we will, at its option, either pay the holder an amount in cash equal to the fractional amount multiplied by the exercise price or round up to the next whole share.

Exercise Limitation

A holder will not have the right to exercise any portion of the Pre-funded Warrant if the holder (together with its affiliates and certain related parties) would beneficially own in excess of 4.99% of the number of shares of our Common Stock outstanding immediately after giving effect to the exercise, as such percentage ownership is determined in accordance with the terms of the 2023 Pre-funded Warrants. However, any holder may increase or decrease such percentage to any other percentage not in excess of 9.99%, provided that any increase in such percentage shall not be effective until 61 days following notice from the holder to us.

Exercise Price

The exercise price per whole share of Common Stock purchasable upon exercise of the 2023 Pre-funded Warrants is $0.001. The exercise price is subject to appropriate adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting our Common Stock and also upon any distributions of assets, including cash, stock or other property to our stockholders.

Transferability

Subject to applicable laws, the 2023 Pre-funded Warrants may be offered for sale, sold, transferred or assigned without our consent.

Exchange Listing

The 2023 Pre-funded 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 Pre-funded Warrants and generally including any reorganization, recapitalization or reclassification of our Common Stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of more than 50% of our outstanding Common Stock, or any person or group becoming the beneficial owner of 50% of the voting power represented by our outstanding Common Stock, the holders of the 2023 Pre-funded Warrants will be entitled to receive upon exercise of the 2023 Pre-funded Warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the 2023 Pre-funded Warrants immediately prior to such fundamental transaction.

Rights as a Stockholder

Except as otherwise provided in the 2023 Pre-funded Warrants or by virtue of such holder's ownership of shares of our Common Stock, the holder of a Pre-funded Warrant does not have the rights or privileges of a holder of our Common Stock, including any voting rights, until the holder exercises the Pre-funded Warrant.

Governing Law

The 2023 Pre-funded Warrants are governed by New York law.

Cash Warrants Issued in January 2023

Exercisability

The warrants issued on January 31, 2023 (the "**2023 Warrants**") 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 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.

Exhibit 21.1

AVENUE THERAPEUTICS, INC.

Subsidiaries of Avenue Therapeutics, Inc. at December 31, 2022, with jurisdiction of incorporation or formation:

- Baergic Bio, Inc. (Delaware)

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the registration statements (No. 333-259850 and No. 333-261520) on Form S-3, (No. 333-219972, No. 333-261710, and No. 333-269689) on Form S-8 and (No. 333-267206) on Form S-1 of our report dated March 31, 2023, with respect to the consolidated financial statements of Avenue Therapeutics, Inc.

/s/ KPMG LLP

New York, New York
March 31, 2023

Exhibit 23.2

Consent of Independent Registered Public Accounting Firm

Avenue Therapeutics, Inc.
Bay Harbor Islands, FL

We hereby consent to the incorporation by reference in the Registration Statements on Form S-1 (No. 333-267206), Form S-3 (No. 333-259850 and No. 333-261520) and Form S-8 (No. 333-219972, No. 333-261710, and No. 333-269689) of Avenue Therapeutics, Inc. of our report dated March 25, 2022, relating to the financial statements which appears in this Annual Report on Form 10-K. Our report contains an explanatory paragraph regarding the Company's ability to continue as a going concern.

/s/ BDO USA, LLP

New York, NY

March 31, 2023

Exhibit 31.1

Certification of Principal Executive Officer
Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934,
As Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Alexandra MacLean, M.D., certify that:

1. I have reviewed this Annual Report on Form 10-K of Avenue Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ Alexandra MacLean, M.D.
Alexandra MacLean, M.D.
Chief Executive Officer
(Principal Executive Officer)
March 31, 2023

Exhibit 31.2

Certification of Principal Financial Officer
Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934,
As Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, David Jin, certify that:

1. I have reviewed this Annual Report on Form 10-K of Avenue Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ David Jin
David Jin
Interim Chief Financial Officer
(Principal Financial Officer)
March 31, 2023

Exhibit 32.1

Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350,
As Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

I, Alexandra MacLean, M.D., Chief Executive Officer of Avenue Therapeutics, Inc. (the "Company"), in compliance with 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, hereby certify that, to the best of my knowledge, the Company's Annual Report on Form 10-K for the period ended December 31, 2022 (the "Report") filed with the Securities and Exchange Commission:

- Fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ Alexandra MacLean, M.D.
Alexandra MacLean, M.D.
Chief Executive Officer
(Principal Executive Officer)
March 31, 2023

Exhibit 32.2

Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350,
As Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

I, David Jin, Interim Chief Financial Officer of Avenue Therapeutics, Inc. (the "Company"), in compliance with 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, hereby certify that, to the best of my knowledge, the Company's Annual Report on Form 10-K for the period ended December 31, 2022 (the "Report") filed with the Securities and Exchange Commission:

- Fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
- The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ David Jin
David Jin
Interim Chief Financial Officer
(Principal Financial Officer)
March 31, 2023