

2024 Annual Report

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, 2024

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 001-37635

AXSOME THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**45-4241907**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
One World Trade Center 22nd Floor New York, New York (Address of principal executive offices)	**10007** (Zip Code)

Registrant's telephone number, including area code: (212) 332-3241

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

Title of each class:	Trading Symbol(s)	Name of Each Exchange on Which Registered
Common Stock, Par Value $0.0001 Per Share (Title of Class)	AXSM	The Nasdaq Global 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 electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T 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 filed, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See 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 (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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

The aggregate market value of voting common stock held by non-affiliates of the registrant (assuming for purposes of this calculation, without conceding, that all executive officers and directors are "affiliates") was approximately $3.2 billion as of June 30, 2024, based on the closing sale price of such stock as reported on The Nasdaq Global Market.

There were 48,765,403 shares of the registrant's common stock outstanding as of February 11, 2025.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy statement for its 2025 Annual Meeting of Stockholders (the "Proxy Statement"), to be filed within 120 days of the registrant's fiscal year ended December 31, 2024, are incorporated by reference in Part III of this Annual Report on Form 10-K. Except with respect to information specifically incorporated by reference in this Annual Report on Form 10-K, the Proxy Statement is not deemed to be filed as part of this Annual Report on Form 10-K.

AXSOME THERAPEUTICS, INC.
ANNUAL REPORT ON FORM 10-K
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2024

TABLE OF CONTENTS

		Page
SPECIAL CAUTIONARY NOTICE REGARDING FORWARD-LOOKING STATEMENTS		3
	PART I	
ITEM 1	Business	4
ITEM 1A	Risk Factors	46
ITEM 1B	Unresolved Staff Comments	104
ITEM 1C	Cybersecurity	104
ITEM 2	Properties	105
ITEM 3	Legal Proceedings	106
ITEM 4	Mine Safety Disclosures	108
	PART II	
ITEM 5	Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	109
ITEM 6	Reserved	110
ITEM 7	Management's Discussion and Analysis of Financial Condition and Results of Operations	111
ITEM 7A	Quantitative and Qualitative Disclosure About Market Risk	126
ITEM 8	Financial Statements and Supplementary Data	126
ITEM 9	Changes in and Disagreements with Accountants on Accounting and Financial Disclosure	126
ITEM 9A	Controls and Procedures	127
ITEM 9B	Other Information	128
ITEM 9C	Disclosure Regarding Foreign Jurisdictions that Prevent Inspections	128
	PART III	
ITEM 10	Directors, Executive Officers and Corporate Governance	129
ITEM 11	Executive Compensation	129
ITEM 12	Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	129
ITEM 13	Certain Relationships and Related Transactions and Director Independence	129
ITEM 14	Principal Accountant Fees and Services	129
	PART IV	
ITEM 15	Exhibits and Financial Statement Schedules	130
ITEM 16	Form 10-K Summary	135
	Signatures	136

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Certain matters discussed in this report, including matters discussed under the caption "Management's Discussion and Analysis of Financial Condition and Results of Operations," may constitute forward-looking statements for purposes of the Securities Act of 1933, as amended, or the Securities Act, and the Securities Exchange Act of 1934, as amended, or the Exchange Act, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from the future results, performance or achievements expressed or implied by such forward-looking statements. The words "anticipate," "believe," "estimate," "may," "expect" and similar expressions are generally intended to identify forward-looking statements. Our actual results may differ materially from the results anticipated in these forward-looking statements due to a variety of factors, including, without limitation, those discussed under the captions "Risk Factors," "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this report, as well as other factors which may be identified from time to time in our other filings with the U.S. Securities and Exchange Commission, or the SEC, or in the documents where such forward-looking statements appear. All written or oral forward-looking statements attributable to us are expressly qualified in their entirety by these cautionary statements. Such forward-looking statements include, but are not limited to, statements about:

- our expectations for increases or decreases in expenses;
- our expectations for the clinical and preclinical development, manufacturing and regulatory approval of our product candidates, and commercialization of our pharmaceutical products or any other products that we may acquire or in-license;
- our estimates of the sufficiency of our existing capital resources combined with future anticipated cash flows to finance our operating requirements;
- our expectations for incurring capital expenditures to expand our research and development and manufacturing capabilities;
- unforeseen circumstances or other disruptions to normal business operations arising from or related to geopolitical conflicts or pandemics;
- our future revenue projections, sales forecasts, and potential peak market data;
- our expectations for generating revenue or becoming profitable on a sustained basis;
- our expectations or ability to enter into marketing and other partnership agreements;
- our expectations or ability to enter into product acquisitions and in-licensing transactions;
- our expectations or ability to build our own commercial infrastructure to manufacture, market and sell our products;
- our expected losses;
- our ability to obtain and maintain intellectual property protection for our products;
- the acceptance of our products by doctors, patients, or payors;
- our stock price and its volatility;
- our ability to attract and retain key personnel;
- the performance of third-party manufacturers;
- our expectations for future capital requirements; and
- our ability to successfully implement our strategy.

The forward-looking statements contained in this report reflect our views and assumptions only as of the date that this report is signed. Except as required by law, we assume no responsibility for updating any forward-looking statements.

We qualify all of our forward-looking statements by these cautionary statements. In addition, with respect to all of our forward-looking statements, we claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

PART I

Unless the context requires otherwise, references in this report to "Axsome," "Company," "we," "us" and "our" and similar designations refer to Axsome Therapeutics, Inc. and our subsidiaries.

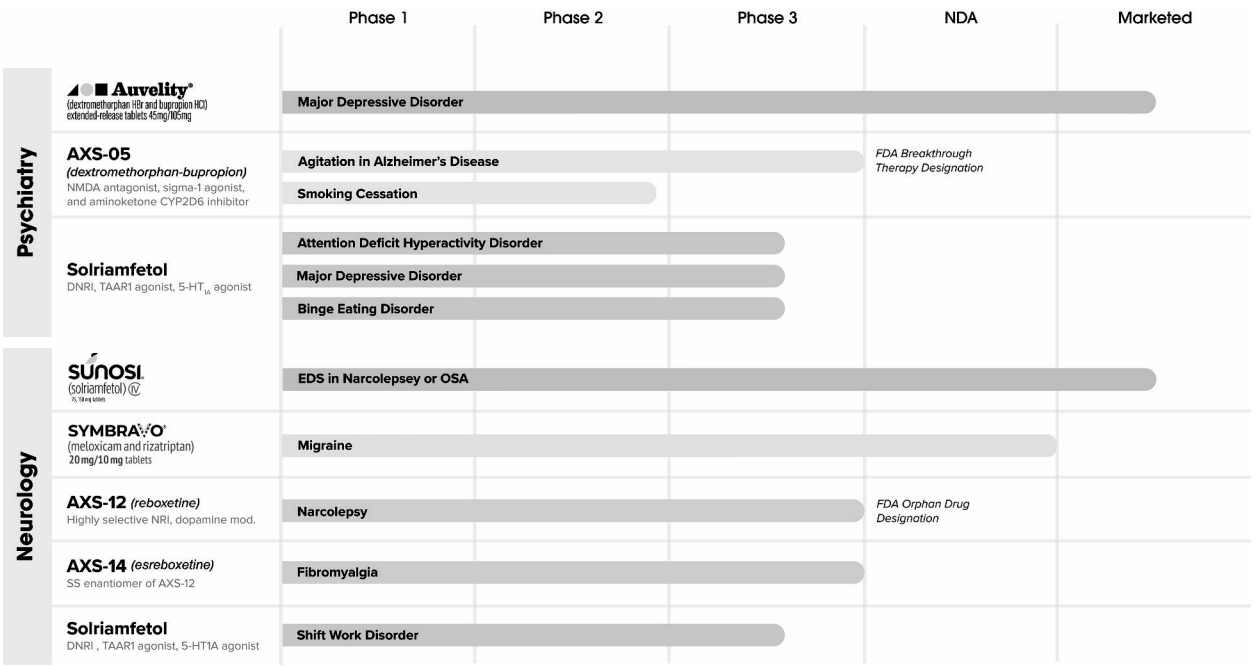
ITEM 1. BUSINESS.

OVERVIEW

We are a biopharmaceutical company dedicated to the development and delivery of transformative medicines for people impacted by central nervous system, or CNS, conditions. We deliver scientific breakthroughs by identifying critical gaps in care and develop differentiated products with a focus on novel mechanisms of action that enable meaningful advancements in patient outcomes. Together, we are on a mission to solve some of the brain's biggest problems so patients and their loved ones can flourish.

Our Pipeline

Our pipeline consists of three commercial products for major depressive disorder, or MDD, and excessive daytime sleepiness, or EDS, associated with narcolepsy and obstructive sleep apnea, our recently FDA-approved product for the acute treatment of migraine, as well as multiple innovative, late-stage, patent-protected product candidates addressing a broad range of serious neurological and psychiatric conditions that collectively impact over 150 million people in the United States. We are leveraging our deep expertise and experience in neuroscience to maximize the potential of our approved products for additional CNS conditions, as well as advance our novel product candidates that we believe may offer distinct advantages over currently available therapies.



Commercial Products

1. **Auvelity®.** Auvelity (dextromethorphan-bupropion) is a novel, oral, N-methyl-D-aspartate (NMDA) receptor antagonist, sigma-1 receptor agonist, aminoketone, and CYP2D6 inhibitor indicated for the treatment of MDD in adults. Auvelity was developed by the Company and approved by the U.S. Food and Drug Administration, or FDA, for the treatment of MDD in adults in August 2022. We initiated the commercial launch of Auvelity in the United States in October 2022. We refer to the proprietary dextromethorphan-bupropion formulation contained in Auvelity as AXS-05. As used in this report, "Auvelity" refers to AXS-05 approved by the FDA for the treatment of MDD in adults, and "AXS-05" refers to AXS-05 in development programs for the treatment of indications beyond MDD in adults.

2. **Sunosi®.** Sunosi (solriamfetol) is a novel, oral, dopamine and norepinephrine reuptake inhibitor (DNRI), trace amine-associated receptor 1 (TAAR1) agonist, and 5-HT_{1A} agonist indicated for the treatment of EDS in patients with narcolepsy or obstructive sleep apnea, or OSA. Sunosi was approved for the treatment of EDS in the United States in 2019 and by the European Commission in 2022. We acquired the U.S. rights to Sunosi from Jazz Pharmaceuticals plc, or Jazz, in May 2022 and the ex-U.S. rights (excluding certain Asian markets) from Jazz in November 2022. We have been commercializing Sunosi since we completed these acquisitions. SK Biopharmaceuticals Co. Ltd., or SK, is the originator of Sunosi and retains rights in 12 Asian markets, including China, Korea, and Japan. We refer to the acquisition of Sunosi herein as the Acquisition. In February 2023, we entered into a licensing agreement, or the Pharmanovia License Agreement, with Atnahs Pharma UK Limited, or Pharmanovia, that granted to Pharmanovia the exclusive right to market Sunosi in Europe and certain countries in the Middle East and North Africa, referred to as the Licensed Territory. As used in this report, "Sunosi" refers to solriamfetol approved for the treatment of EDS in patients with narcolepsy or OSA, and "solriamfetol" refers to solriamfetol in development programs for the treatment of indications beyond EDS in patients with narcolepsy or OSA.

3. **Symbravo®.** Symbravo (MoSEIC™ meloxicam rizatriptan), or AXS-07, is a novel, oral, rapidly absorbed, multi-mechanistic, selective COX-2 inhibitor and 5-$HT_{1B/1D}$ agonist indicated for the acute treatment of migraine with or without aura. Symbravo was developed by the Company and approved by the FDA for the acute treatment of migraine with or without aura in adults in January 2025.

Development Programs

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational NMDA receptor antagonist, sigma-1 receptor agonist, aminoketone, and CYP2D6 inhibitor being developed for the treatment of Alzheimer's disease agitation, or AD agitation, and smoking cessation. AXS-05 utilizes a proprietary formulation and dose of dextromethorphan and bupropion, and Axsome's metabolic inhibition technology, to modulate the delivery of the components. AXS-05 has been granted FDA Breakthrough Therapy designation for AD agitation. In December 2024, we announced the successful completion of our Phase 3 clinical program of AXS-05 in AD agitation, which consists of the ADVANCE-1 Phase 2/3 trial, ADVANCE-2 Phase 3 trial, ACCORD-1 Phase 3 trial, and ACCORD-2 Phase 3 trial evaluating the efficacy and safety of AXS-05 in patients with AD agitation, as well as an open-label extension trial evaluating the long-term safety of AXS-05. A positive Phase 2 trial of AXS-05 in smoking cessation has been completed under a research collaboration with Duke University.

AXS-12 (reboxetine) is a novel, oral, investigational, highly selective and potent norepinephrine reuptake inhibitor and cortical dopamine modulator being developed for the treatment of narcolepsy. AXS-12 has been granted FDA Orphan Drug Designation for narcolepsy. Our clinical program for AXS-12 in narcolepsy includes our completed positive CONCERT Phase 2 trial and SYMPHONY Phase 3 trial evaluating the efficacy and safety of AXS-12 compared to placebo, as well as our completed positive ENCORE Phase 3 trial evaluating the long-term efficacy and safety of AXS-12 in patients with narcolepsy with cataplexy.

AXS-14 (esreboxetine) is a novel, oral, investigational, highly selective and potent norepinephrine reuptake inhibitor being developed for the management of fibromyalgia. Esreboxetine, the SS-enantiomer of reboxetine, is more potent and selective than racemic reboxetine. We have in-licensed data from Pfizer Inc., or Pfizer, which includes a completed positive Phase 2 and Phase 3 trial in fibromyalgia.

Solriamfetol is an oral, DNRI, TAAR1 agonist, and 5-HT1A agonist being developed for the treatment of attention deficit hyperactivity disorder, or ADHD, major depressive disorder, or MDD, binge eating disorder, or BED, and excessive sleepiness associated with shift work disorder, or SWD. We are currently conducting four Phase 3, randomized, double-blind, placebo-controlled, multicenter trials evaluating the efficacy and safety of solriamfetol in each of these indications, including the FOCUS study in ADHD, the PARADIGM study in MDD, the ENGAGE study in BED, and the SUSTAIN study in SWD.

Additionally, we are currently evaluating other product candidates that we intend to develop for CNS disorders. We aim to become a fully integrated biopharmaceutical company that develops and commercializes differentiated therapies that increase available treatment options and improve the lives of patients living with CNS disorders.

Our product candidates are protected by a combination of patents, trade secrets, and proprietary know-how. If approved, they may also be eligible for periods of regulatory exclusivity. Our intellectual property portfolio includes issued U.S. and foreign patents with claims extending to 2034, 2040, 2041, and 2043 for AXS-05 and to 2039 for AXS-12, as well as U.S. and foreign patent applications for AXS-05, AXS-12, and AXS-14. Our issued U.S. and foreign patents for Symbravo include claims extending out to 2040. Our Orange Book listed patents in the United States for Sunosi extend out to 2042. We also have patents in various other countries pertaining to Sunosi. In June 2024, we entered into a settlement agreement with Unichem Laboratories Ltd., or Unichem, resolving patent litigation related to Sunosi that permits Unichem to begin selling its generic version of Sunosi on June 30, 2042, or earlier under certain circumstances. In August 2024, we reached an agreement with Sandoz Inc., or Sandoz, to dismiss the patent litigation related to Sunosi following Sandoz's withdrawal of its Abbreviated New Drug Application, or ANDA, for a generic equivalent of Sunosi. As a result, the litigation has been dismissed without prejudice. In February 2025, we entered into a settlement agreement resolving all outstanding patent litigation related to Auvelity. The litigation resulted from submission by Teva of an ANDA to the FDA seeking approval to market a generic version of Auvelity in the U.S. prior to the expiration of applicable Axsome patents. Under the terms of the settlement agreement, Axsome will grant Teva a license to sell its generic version of Auvelity beginning on or after March 31, 2039, if pediatric exclusivity is granted, or on or after September 30, 2038, if no pediatric exclusivity is granted, subject to FDA approval and conditions and exceptions customary for agreements of this type.

Our Strategy

Our goal is to efficiently develop and commercialize novel, differentiated therapies for the treatment of CNS disorders. The primary elements of our strategy to achieve this goal are the following:

- ***Pursue novel CNS indications with high unmet medical need.*** We believe that CNS disorders are significantly underserved therapeutic segments with currently limited treatment options. We are developing our product candidates for CNS indications where there exist significant unmet medical needs, or that have no or few FDA-approved pharmacological treatments. CNS disorders are often disabling, difficult to treat, and associated with significant comorbidities. By focusing on areas of unmet medical need, we aim to develop products that have the potential to change current medical practice, and that are highly relevant to patients, physicians, and regulatory bodies. Many of these indications have significant patient populations, which, when combined with the limitations of current treatments, should provide us with attractive commercial opportunities.

- ***Develop products with our proprietary medicinal chemistry and formulation technologies.*** Our proprietary medicinal chemistry and formulation technologies allow us to continue to design new and innovative medicines to treat CNS conditions. These technologies and capabilities include: (1) chiral chemistry and formulation to identify, isolate and stabilize chirally pure enantiomers, (2) metabolic inhibition as a novel drug delivery method to increase the bioavailability and prolong the half-life of target drug molecules, (3) the MoSEIC™, or Molecular Solubility Enhanced Inclusion Complex, technology which is designed to substantially increase the solubility and speed the absorption of target drug molecules, and (4) proprietary chemical synthesis and analysis to produce target drug molecules.

- ***Develop products with differentiated profiles.*** We aim to develop products with novel mechanisms of action for the intended indications that may yield differentiated product profiles. For example, AXS-05 combines several mechanisms of action resulting in a unique pharmacological profile that may be relevant to the treatment of numerous CNS disorders. The MoSEIC™ technology is designed to improve the absorption of drug molecules after oral administration and is utilized in Symbravo (AXS-07). We believe that products with clearly differentiated features will be attractive to patients and their physicians and will provide us with a competitive commercial advantage.

- ***Reduce clinical and regulatory risk, limit development costs, and accelerate time to market.*** Some of our product candidates incorporate chemical entities with long histories of clinical use and well characterized safety profiles. Use of well characterized molecules has allowed us to rapidly complete early clinical development of our product candidates and may reduce the risk of late-stage clinical failures due to unexpected toxicities. This strategy may allow us to seek FDA approval for some of our product candidates using the 505(b)(2) regulatory pathway. Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, or FDCA, permits an applicant to file a new drug application, or NDA, that relies, in part, on the FDA's prior findings of safety and efficacy in the approval of a similar drug, or on published literature. It therefore allows us to leverage previous preclinical and clinical experience with the active molecules in some of our product candidates and potentially forego conducting certain lengthy and costly preclinical studies, reduce clinical and regulatory risk, limit development costs, and accelerate our time to commercialization.

- ***Retain commercial rights in the United States, where appropriate, and selectively partner outside of the United States to maximize the value of our product candidates.*** We intend to commercialize our product candidates, if approved, in the United States through the establishment of our own focused, cost-effective sales and marketing organization. We intend to selectively partner commercial rights outside of the United States with third parties to maximize the value of our product candidates without the substantial investment required to develop independent sales forces in those geographies. We continue to evaluate strategic options for the commercialization of our other product candidates.

CNS Product Candidates

AXS-05

Overview

AXS-05 (dextromethorphan-bupropion) is a novel, oral, investigational NMDA receptor antagonist, sigma-1 receptor agonist, aminoketone, and CYP2D6 inhibitor being developed for the treatment of CNS disorders. AXS-05 consists of a proprietary formulation and dose of dextromethorphan and bupropion and utilizes Axsome's metabolic inhibition technology. The dextromethorphan component of AXS-05 is an uncompetitive antagonist of the NMDA receptor, an ionotropic glutamate receptor, and a sigma-1 receptor agonist. Dextromethorphan is quickly eliminated from the body following administration due to extensive first pass metabolism, which results in low blood levels even at high doses. The bupropion component of AXS-05 serves to increase the bioavailability of dextromethorphan by inhibiting its metabolism and is also a dopamine and norepinephrine reuptake inhibitor (DNRI). Based on its unique mechanism of action with multimodal activity, we believe that AXS-05 has potential therapeutic benefit for a variety of CNS disorders.

We are currently developing AXS-05 for the treatment of AD agitation and smoking cessation.

Alzheimer's Disease (AD) Agitation

AD is an irreversible, progressive neurodegenerative disorder that manifests initially as forgetfulness and advances to severe cognitive impairment and memory loss. It is the most common form of dementia, affecting approximately 7 million people in the United States, a number that is anticipated to double by 2060. Approximately 70% of AD patients experience agitation, which is characterized by emotional distress, verbal and physical aggressiveness, disruptive irritability, and disinhibition. AD agitation is associated with increased caregiver burden, decreased functioning, earlier institutionalization, and death.

There is only one FDA-approved pharmacological treatment for the treatment of AD agitation. Currently, AD patients with agitation are often treated with antipsychotic medications despite black box warnings for the use of these medications in this patient population. Typical antipsychotics prescribed for agitation, aggression, or insomnia are associated with functional decline, extrapyramidal symptoms, cardiovascular effects, and sedation in patients with AD, while studies indicate that atypical antipsychotics may be associated with increased rates of cerebrovascular events and death in patients with dementia.

In June 2020, we announced that AXS-05 had received FDA Breakthrough Therapy designation for AD agitation. In August 2020, we announced confirmation of the pivotal development status and plan for AXS-05 for the treatment of AD agitation following a Breakthrough Therapy meeting with the FDA. In December 2024, we announced the successful completion of our Phase 3 clinical program of AXS-05 in AD agitation, which consists of the ADVANCE-1 Phase 2/3 trial, ADVANCE-2 Phase 3 trial, ACCORD-1 Phase 3 trial, and ACCORD-2 Phase 3 trial evaluating the efficacy and safety of AXS-05 in patients with AD agitation, as well as an open-label extension trial evaluating the long-term safety of AXS-05 in AD agitation.

ADVANCE-1 Study

In July 2017, we initiated the ADVANCE-1 study, a Phase 2/3, randomized, double-blind, controlled, multicenter U.S. trial to evaluate the efficacy and safety of AXS-05 in patients with AD agitation. A total of 366 patients with a diagnosis of probable AD and clinically meaningful agitation associated with their AD were 1:1 randomized to receive AXS-05 (dextromethorphan-bupropion tablet, dose escalated to 45 mg-105 mg twice daily), bupropion (dose escalated to 105 mg twice daily), or matching placebo for 5 weeks. An independent data monitoring committee performed an interim futility analysis and recommended no further randomization to the bupropion arm. Subsequently, patients were 1:1 randomized to receive AXS-05 or placebo. The primary endpoint was the change from baseline in the Cohen-Mansfield Agitation Inventory, or CMAI, total score compared to placebo at Week 5. In April 2020, we announced that AXS-05 achieved the primary endpoint and rapidly and substantially improved agitation in patients with AD.

AXS-05 met the primary endpoint by demonstrating a statistically significant mean reduction in the CMAI total score compared to placebo at Week 5, with mean reductions from baseline of 15.4 points for AXS-05 and 11.5 points for placebo ($p=0.010$). These results represent a mean percentage reduction from baseline of 48% for AXS-05 compared to 38% for placebo. AXS-05 was also superior to bupropion on the CMAI total score ($p<0.001$), establishing component contribution. Improvement on the CMAI total score numerically favored AXS-05 over placebo starting as early as Week 2 and achieved statistical significance by Week 3 ($p=0.007$), only one week after full dosing with AXS-05.

Additionally, a statistically significantly greater proportion of patients in the AXS-05 group achieved a clinical response on the CMAI, defined as a 30% or greater improvement from baseline, compared to placebo at Week 5 (73% for AXS-05 vs. 57% for placebo, $p=0.005$). Consistent with these results, AXS-05 demonstrated a statistically significantly greater improvement in agitation as measured by clinicians' global assessments of change measured using the modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change for Agitation, or mADCS-CGIC, compared to placebo ($p=0.036$).

AXS-05 was well tolerated in the ADVANCE-1 trial. The most common adverse events were somnolence (8.2% for AXS-05 vs. 4.1% for bupropion vs. 3.2% for placebo), dizziness (6.3% for AXS-05 vs. 10.2% for bupropion vs. 3.2% for placebo), and diarrhea (4.4% for AXS-05 vs. 6.1% for bupropion vs. 4.4% for placebo). Discontinuation rates due to adverse events were low and balanced among treatment groups (1.3% for AXS-05 vs. 2.0% for bupropion vs. 1.3% for placebo). Serious adverse events were reported in 3.1% of patients in the AXS-05 group, 8.2% of patients in the bupropion group, and 5.7% of patients in the placebo group, none of which were deemed related to the study drug. There were no deaths in the AXS-05 group, one death in the bupropion group, and one death in the placebo group. AXS-05 was not associated with sedation or cognitive decline as measured by the Mini-Mental State Examination, or MMSE.

ACCORD-1 Study

In December 2020, we initiated the ACCORD-1 study, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of AXS-05 in patients with AD agitation. The trial consisted of a 9-week, open-label period during which patients were treated with AXS-05 and monitored for a sustained clinical response, followed by a 26-week, double-blind, placebo-controlled, randomized withdrawal period. Sustained clinical response was defined as a ≥30% improvement from baseline in the CMAI total score and improvement on the Patient Global Impression of Change, or PGI-C, scale (score of ≤3) that were maintained for at least 4 consecutive weeks. A total of 178 patients were enrolled into the open-label period and treated with AXS-05, and 108 patients were 1:1 randomized to continue AXS-05 (n=53) or to switch to placebo (n=55) for up to 26 weeks or until a relapse of agitation occurred. Relapse was defined as a ≥10-point worsening in the CMAI total score from randomization, or a CMAI total score greater than that at study entry, or hospitalization or other institutionalization due to AD agitation. The primary endpoint was the time from randomization to relapse of AD agitation calculated by Kaplan-Meier estimates and the hazard ratio. Secondary assessments included the CMAI, clinician- and caregiver-rated scales, and safety parameters. The key secondary endpoint was the percentage of patients who relapsed compared to placebo.

In November 2022, we announced that AXS-05 achieved the primary endpoint in the ACCORD-1 Phase 3 trial by substantially and statistically significantly delaying the time to relapse of AD agitation compared to placebo, with a hazard ratio for time to relapse of 0.275 (p=0.014), representing a 3.6-fold lower risk of relapse compared to placebo. AXS-05 also met the key secondary endpoint by statistically significantly preventing relapse of AD agitation compared to placebo, with 7.5% of patients in the AXS-05 group relapsing compared to 25.9% of patients in the placebo group (p=0.018). In the open-label treatment period, AXS-05 demonstrated a rapid, substantial, and statistically significant improvement in AD agitation compared to baseline as measured by the CMAI total score, starting at Week 1 and continuing throughout at all timepoints (p<0.001). Additionally, rapid and substantial improvement in AD agitation was reported by both clinicians and caregivers on global measures. Clinicians reported improvement in AD agitation with open-label AXS-05 treatment in 66% of patients at 2 weeks and 86% at 5 weeks as measured by the mADCS-CGIC scale. Caregivers reported improvement in AD agitation in 68% of patients at 2 weeks and 89% at 5 weeks as measured by the PGI-C scale.

AXS-05 was well tolerated in the ACCORD-1 trial. The rates of adverse events in the double-blind period were 28.3% in the AXS-05 group and 22.2% in the placebo group. Discontinuation rates due to adverse events were low (0% for AXS-05 vs. 1.9% for placebo). One serious adverse event was reported in the AXS-05 group (faecaloma), which was determined by the investigator to be not related to the study drug, and two serious adverse events were reported in the placebo group (cardiac arrest, femur fracture). Falls were reported in four patients in the AXS-05 group, none of which were associated with serious adverse events and all of which were determined by the investigators to be not related to the study drug, and in two patients in the placebo group, one of which was associated with a femur fracture. There were no deaths in the AXS-05 group and one death in the placebo group. AXS-05 was not associated with sedation or cognitive decline as measured by the MMSE.

ADVANCE-2 Study

In September 2022, we initiated the ADVANCE-2 study, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of AXS-05 in patients with AD agitation. A total of 408 patients were 1:1 randomized to receive AXS-05 (dextromethorphan-bupropion tablet, dose escalated to 45 mg-105 mg twice daily) or matching placebo for 5 weeks. In December 2024, we announced topline results from the ADVANCE-2 trial. AXS-05 did not achieve statistical significance for the primary endpoint, the change in the CMAI total score compared to placebo at Week 5, with mean reductions from baseline of 13.8 points for AXS-05 and 12.6 points for placebo. However, results for the primary and nearly all secondary endpoints numerically favored AXS-05 placebo at all time points in the trial.

AXS-05 was safe and well tolerated in the ADVANCE-2 trial. The rates of adverse events in the trial were 26.0% in the AXS-05 group and 21.6% in the placebo group. The most common adverse events were dizziness (5.9% for AXS-05 vs. 1.5% for placebo) and headache (4.4% for AXS-05 vs. 3.4% for placebo). Falls were reported in one patient (0.5%) in the AXS-05 group, which was determined by the investigator to be not related to study drug, and one patient (0.5%) in the placebo group. Two patients in the AXS-05 group reported three serious adverse events, none of which were determined by the investigators to be related to study drug (asthenia, urinary tract infection, and cerebrovascular accident). Discontinuation rates due to adverse events were low (1.5% for AXS-05 vs. 0% for placebo). There were no deaths in the trial, and AXS-05 was not associated with sedation or cognitive decline as measured by the MMSE.

ACCORD-2 Study

In May 2024, we announced that we had initiated the ACCORD-2 study, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of AXS-05 in patients with AD agitation. The trial consisted of an open-label treatment period followed by a 24-week, double-blind, placebo-controlled, randomized withdrawal period. A total of 167 patients, who rolled over from the open-label extension trial of AXS-05, experienced a sustained clinical response with AXS-05 and were 1:1 randomized to continue AXS-05 (n=83) or to switch to placebo (n=84). Treatment was continued for up to 24 weeks or until a relapse of agitation occurred. The primary endpoint was the time from randomization to relapse of AD agitation calculated by Kaplan-Meier estimates and the hazard ratio. The key secondary endpoint was the percentage of patients who relapsed compared to placebo.

In December 2024, we announced that AXS-05 achieved the primary endpoint in the ACCORD-2 Phase 3 trial and demonstrated a highly statistically significant delay in the time to relapse of AD agitation compared to placebo, with a hazard ratio for time to relapse of 0.276 (p=0.001), representing a 3.6-fold lower risk of relapse compared to placebo. AXS-05 also met the key secondary endpoint by statistically significantly preventing relapse of AD agitation compared to placebo, with 8.4% of patients in the AXS-05 group relapsing compared to 28.6% of patients in the placebo group (p=0.001). Additionally, AXS-05 substantially and statistically significantly prevented worsening of overall Alzheimer's disease severity compared to placebo as measured by the Clinical Global Impression of Severity, or CGI-S, scale for Alzheimer's disease, with 13.3% of patients in the AXS-05 group worsening on the CGI-S for Alzheimer's disease overall clinical status compared to 39.3% of patients who switched to placebo (p<0.001).

In the open-label period, treatment with AXS-05 was associated with a 20.4-point reduction in the CMAI total score at 6 weeks, representing a 46% reduction from the mean baseline score. Additionally, substantial improvement in AD agitation was reported by both clinicians and caregivers on global measures. Clinicians reported improvement in AD agitation with open-label AXS-05 treatment in 78% of patients at 8 weeks as measured by the mADCS-CGIC scale. Caregivers reported improvement in AD agitation in 71% of patients at 4 weeks and 78% of patients at 8 weeks as measured by the PGI-C scale. Of the patients treated for at least 8 weeks during the open-label period, 70% experienced a sustained clinical response and were randomized in the double-blind period.

AXS-05 was safe and well tolerated in the ACCORD-2 trial. The rates of adverse events in the double-blind period were 29.3% in the AXS-05 group and 32.1% in the placebo group, with no individual adverse event occurring in more than 3.7% of patients. Discontinuation rates due to adverse events were low (0% for AXS-05 vs. 1.2% for placebo). There were two serious adverse events reported in the trial, both of which occurred in the placebo group (cellulitis and urinary retention). Falls were reported in two patients (2.4%) in the AXS-05 group, only one of which was determined by the investigator to be related to study drug. There were no deaths in the trial, and AXS-05 was not associated with sedation or cognitive decline as measured by the MMSE.

Long-Term Safety Study

In December 2024, we announced topline results from the open-label extension trial evaluating the long-term safety and tolerability of AXS-05 in patients with AD agitation. A total of 456 patients were treated with AXS-05 for up to 12 months. AXS-05 was well tolerated with long-term dosing, with a safety profile consistent with the controlled efficacy and safety trials. The rate of adverse events in the trial was 39.9%, with headache (5.5%) being the only adverse event reported in ≥5% of patients. Discontinuations due to adverse events with long-term dosing were low (0.7%). Falls were reported in 3.1% of patients, with only 0.2% deemed to be related to the study drug. There were no deaths in the trial, and AXS-05 was not associated with sedation or cognitive decline as measured by the MMSE.

Smoking Cessation

We are also evaluating AXS-05 as an aid to smoking cessation treatment. Over 34 million adults in the U.S. smoke cigarettes, 50% of whom live with a smoking-related disease. Approximately 70% of smokers report that they want to quit, but only an estimated 3-5% who attempt to quit without assistance are successful for 6-12 months, and even with the currently available treatment options, relapse rates remain above 80%. Tobacco use results in approximately 500,000 premature deaths each year in the U.S., according to the Centers for Disease Control and Prevention. Smoking is the single largest cause of preventable disease and death in the U.S., accounting for nearly 1 in 5 deaths. Direct health care and lost productivity costs as a result of smoking total approximately $300 billion annually in the U.S. alone.

In December 2017, we entered into a research collaboration agreement with Duke University to evaluate AXS-05 in a Phase 2 clinical trial in smoking cessation under an Investigator Sponsored Investigational New Drug Application, or IND. In April 2018, we announced the enrollment of the first patient into a Phase 2 clinical trial of AXS-05 for smoking cessation treatment, which was being conducted under our research collaboration agreement with Duke University. In April 2019, we announced that AXS-05 met the prespecified primary endpoint in the Phase 2 trial in smoking cessation. In November 2021, we announced that we had received from the FDA positive Pre-Investigational New Drug Application, or Pre-IND, meeting written guidance on a proposed clinical developmental plan for AXS-05 as an aid to smoking cessation. Based on this feedback, Axsome plans to proceed to a pivotal Phase 2/3 trial in this indication.

AXS-12

Overview

AXS-12 (reboxetine) is a novel, oral, potent, highly selective investigational norepinephrine reuptake inhibitor and cortical dopamine modulator being developed for the treatment of narcolepsy.

In October 2018, we received Orphan Drug Designation from the FDA for AXS-12 for the treatment of narcolepsy. In January 2020, we entered into an exclusive license agreement with Pfizer for Pfizer's clinical and nonclinical data, and intellectual property for reboxetine, the active pharmaceutical ingredient in AXS-12. In September 2020, we announced that the Phase 2 CONCERT study and a single Phase 3 study would be sufficient to support the filing of an NDA. In July 2021, we announced that we were notified by the FDA that the FDA had rescinded our Breakthrough Therapy Designation for AXS-12 for the treatment of cataplexy in narcolepsy, due to the FDA's approval of an additional drug product for the treatment of cataplexy in narcolepsy subsequent to their granting AXS-12 Breakthrough Therapy designation.

Narcolepsy

Narcolepsy is a serious and debilitating orphan neurological condition that causes dysregulation of the sleep-wake cycle and is characterized clinically by EDS, cataplexy, hypnagogic hallucinations, sleep paralysis, and disrupted nocturnal sleep. Narcolepsy afflicts an estimated 185,000 individuals in the U.S. Cataplexy is seen in an estimated 70% of narcolepsy patients and is characterized by a sudden reduction or loss of muscle tone while a patient is awake, typically triggered by strong emotions such as laughter, fear, anger, stress, or excitement. Narcolepsy is a life-long condition that interferes with cognitive, psychological, and social functioning, increases the risk of work- and driving-related accidents, and is associated with a 1.5-fold higher mortality rate.

Our clinical program for AXS-12 in narcolepsy includes our completed positive CONCERT Phase 2 trial and SYMPHONY Phase 3 trial evaluating the efficacy and safety of AXS-12 compared to placebo, as well as our completed positive ENCORE Phase 3 trial evaluating the long-term efficacy and safety of AXS-12 in patients with narcolepsy with cataplexy.

CONCERT Study

In January 2019, we initiated the CONCERT study to evaluate the efficacy and safety of AXS-12 in narcolepsy. In December 2019, we announced that AXS-12 met the prespecified primary endpoint and significantly reduced the total number of cataplexy attacks compared to placebo.

CONCERT was a Phase 2, randomized, double-blind, placebo-controlled, crossover, multicenter, U.S. trial in which 21 patients with a diagnosis of narcolepsy with cataplexy were all treated with orally administered AXS-12 for 2 weeks, and with placebo for 2 weeks, with the treatment periods separated by 1 week of down-titration and washout.

AXS-12 met the prespecified primary endpoint by demonstrating a highly statistically significant reduction from baseline in the mean weekly number of cataplexy attacks, averaged for the 2-week treatment period, the overall treatment effect, compared to placebo ($p<0.001$). At Week 2, AXS-12 demonstrated a mean reduction of 14.6 cataplexy attacks per week compared to a reduction of 2.6 attacks per week for placebo ($p=0.002$), representing mean reductions of 48.8% and 8.6% from baseline, respectively. The proportion of patients achieving a 50% or greater reduction in the weekly number of cataplexy attacks was 76.2% for AXS-12, compared to 30.0% for placebo at Week 2 ($p=0.003$). The improvement in cataplexy was rapid, with AXS-12 demonstrating significant benefit over placebo as early as Week 1 ($p<0.001$).

AXS-12 significantly improved EDS symptoms compared to placebo, as measured by the Epworth Sleepiness Scale, or ESS, and by the frequency of inadvertent naps. The improvement on the ESS with AXS-12 treatment was twice that observed with placebo, with reductions from baseline in the ESS score of 6.0 and 3.1, respectively for AXS-12 and placebo ($p=0.003$). AXS-12 treatment resulted in a 31.8% mean reduction from baseline in the average weekly number of inadvertent naps compared to a 5.3% mean reduction for placebo at Week 2 ($p<0.001$). Improvement in the frequency of inadvertent naps was rapid, with AXS-12 demonstrating significant benefit over placebo as early as Week 1 ($p=0.038$).

AXS-12 significantly improved cognitive function compared to placebo over the 2-week treatment period as measured by the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire, or NSAQ, which was assessed daily ($p<0.001$). For this assessment, patients rated their ability to concentrate on a 5-point scale (1=very good to 5=very poor). At the end of treatment, 42.9% of patients had an ability to concentrate that was "good" to "very good" with AXS-12 treatment, compared to 25.0% of patients with placebo, and 0% of patients at baseline. The improvement in the ability to concentrate was rapid, with AXS-12 demonstrating significant improvement over placebo as early as Week 1 ($p=0.007$).

AXS-12 significantly improved sleep quality, as measured by overall improvement and by number of awakenings at night, and reduced sleep-related symptoms, compared to placebo. AXS-12 treatment resulted in 45.0% of patients reporting improved sleep quality compared to 5.3% of patients with placebo (p=0.007). AXS-12 treatment resulted in 30.0% of patients reporting a reduction in the number of awakenings at night compared to 5.3% of patients with placebo (p=0.044). AXS-12 treatment also resulted in greater proportions of patients with reductions in sleep paralysis episodes, and in hypnagogic hallucinations, compared to placebo (p=ns).

AXS-12 was well tolerated in the trial. The most common adverse events in the AXS-12 group were anxiety, constipation, and insomnia.

SYMPHONY Study

In September 2021, we enrolled the first patient in SYMPHONY study, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial evaluating the efficacy and safety of AXS-12 in patients with narcolepsy. A total of 90 patients were 1:1 randomized to receive AXS-12 or placebo for 5 weeks. Patients took either AXS-12 (5 mg) or placebo once daily during Week 1 followed by twice daily dosing during Weeks 2-5. The primary endpoint was the change in frequency of weekly cataplexy attacks. Other symptoms of narcolepsy as well as safety and tolerability were also assessed in the trial. In March 2024, we announced that AXS-12 achieved the primary endpoint in the SYMPHONY Phase 3 trial and statistically significantly reduced the frequency of cataplexy attacks in patients with narcolepsy compared to placebo. AXS-12 also reduced EDS severity, improved cognitive function, and reduced overall narcolepsy severity compared to placebo.

AXS-12 met the primary endpoint by demonstrating a substantial and statistically significant reduction from baseline in weekly cataplexy attacks compared to placebo at Week 5, with reductions of 83% for AXS-12 and 66% for placebo (p=0.018). AXS-12 rapidly reduced weekly cataplexy attacks, demonstrating a reduction of 56% compared to 31% for placebo at Week 1 (p=0.007). Additionally, AXS-12 resulted in remission of cataplexy and increased cataplexy-free days compared to placebo. Remission of cataplexy, defined as a 100% reduction from baseline, was achieved by 33% of AXS-12 patients compared to 9.5% of placebo patients at Week 5 (p=0.008). Achievement of remission was rapid, with 24% of AXS-12 patients achieving remission at Week 2 compared to 4.5% of placebo patients (p=0.008). AXS-12 increased the percentage of cataplexy-free days per week, defined as days with zero cataplexy attacks, to 84.5% at Week 5 compared to 22.6% for placebo (p=0.014).

AXS-12 significantly reduced EDS severity as measured by the CGI-S scale for EDS compared to placebo at Week 5, with mean reductions of 1.8 points for AXS-12 compared to 0.9 points for placebo (p=0.027). Statistical significance was observed as early as Week 1 (p=0.006). Concurrent EDS and cataplexy response was achieved by 57% of patients in the AXS-12 group compared to 33% of patients in the placebo group at Week 5 (p=0.029). Response was defined as a ≥30% reduction in inadvertent naps and a ≥50% reduction in cataplexy attacks, respectively. The improvement in frequency of inadvertent naps was rapid, with 54% of patients in the AXS-12 group experiencing a decrease in the number of inadvertent naps compared to 28% of patients in the placebo group, as measured by the NSAQ, at Week 5 (p=0.016).

AXS-12 significantly improved concentration and memory compared to placebo at Week 5 as measured by the Cognitive Function Items of the Functional Outcomes of Sleep Questionnaire, or FOSQ-10, (p=0.004). Concurrent cognitive and cataplexy response was achieved by 41% of patients in the AXS-12 group compared to 17% of patients in the placebo group at Week 5 (p=0.016). Response was defined by an increase in days patients rated their Ability to Concentrate as very good or good and a ≥50% reduction in cataplexy attacks, respectively.

AXS-12 also demonstrated improvements in overall narcolepsy, patient function, and quality of life. Clinicians reported a rapid and significant reduction in overall narcolepsy severity in patients in the AXS-12 group compared to patients in the placebo group, as measured by the CGI-S for narcolepsy, at Week 5 (p=0.007), with improvements observed as early as Week 1 (p<0.001). Statistically significant improvements in overall patient function and quality of life as measured by the FOSQ-10 total score was observed with AXS-12 compared to placebo at Week 5 (p=0.005).

ENCORE Study

In October 2021, we initiated the ENCORE study, a Phase 3, randomized, double-blind, placebo-controlled trial to evaluate the long-term efficacy and safety of AXS-12 in patients with narcolepsy. The trial consisted of a 24-week open-label treatment period followed by a 3-week, double-blind, randomized withdrawal period. A total of 68 patients, who rolled over from the SYMPHONY Phase 3 trial, were enrolled into the open-label period and treated with AXS-12 (5 mg) once-daily for the first week, followed by twice-daily dosing for the subsequent 23 weeks. Patients who completed the open-label treatment period (n=42) were then 1:1 randomized to continue AXS-12 (n=22) or to switch to placebo (n=20). The primary endpoint was the change in frequency of weekly cataplexy attacks from randomization to week 3 of the double-blind period. Other symptoms of narcolepsy as well as safety and tolerability were also assessed throughout the trial. In March 2024, we announced that AXS-12 achieved the primary endpoint in the SYMPHONY Phase 3 trial and statistically significantly reduced the frequency of cataplexy attacks in patients with narcolepsy compared to placebo. AXS-12 also reduced EDS severity, improved cognitive function, and reduced overall narcolepsy severity compared to placebo.

AXS-12 met the primary endpoint of the change from randomization in the frequency of cataplexy attacks compared to placebo at week 3 of the double-blind period. Patients randomized to switch to placebo experienced a statistically significant worsening in the average weekly number of cataplexy attacks compared to patients randomized to continue AXS-12 treatment, with an increase of 10.29 attacks per week for placebo compared to 1.32 attacks per week for AXS-12, at 3 weeks (p=0.017). Additionally, AXS-12 demonstrated a statistically significant improvement in cognitive function compared to placebo at Week 5 as measured by the NSAQ and the PGI-C. A significantly greater percentage of patients who switched to placebo experienced worsening in the NSAQ Ability to Concentrate item compared to those who continued AXS-12 treatment at 3 weeks (52.6% for placebo vs. 14.3% for AXS-12, p=0.011). A significantly greater percentage of patients who switched to placebo also reported worsening in their ability to concentrate compared to patients who continued AXS-12 treatment at 3 weeks (57.9% for placebo vs. 22.2% for AXS-12, p=0.029). Additionally, AXS-12 demonstrated improvements in overall narcolepsy as measured by the PGI-C scale. A significantly greater percentage of patients who switched to placebo reported worsening of their narcolepsy compared to those who continued AXS-12 treatment at 3 weeks (52.6% for placebo vs. 16.7% for AXS-12, p=0.024).

In the open-label period, treatment with AXS-12 led to substantial and sustained improvement of cataplexy, with patients experiencing a 71% reduction from baseline in mean weekly cataplexy attacks at 1 month, which was sustained with long-term treatment, resulting in a 77% reduction at 6 months. Cataplexy response, defined as ≥50% reduction from baseline in weekly cataplexy attacks, was achieved by 72% of patients at 1 month, and by 82% of patients at 6 months with AXS-12 treatment. Treatment with AXS-12 also substantially increased the percentage of cataplexy-free days (days with zero cataplexy attacks) per week from 14% at baseline to 61% at 1 month and 70% at 6 months.

Long-term open-label treatment with AXS-12 resulted in substantial improvements in EDS, assessed using the ESS and the Clinician Global Impression of Change, or CGI-C, scale. Mean ESS scores were reduced by 5.6 points at 1 month, with the improvement maintained with long-term treatment resulting in a mean reduction of 7.3 points at 6 months. Clinicians reported improvement in EDS in a substantial proportion of patients on the CGI-C scale, with 84% of patients achieving EDS improvement at 1 month and 78% of patients at 6 months. A substantial proportion of patients reported improvement in cognition which was sustained with long-term open-label treatment. Improvement in cognition, assessed by the NSAQ Ability to Concentrate item, was reported by 55% of patients at 1 month and 59% at 6 months with AXS-12 treatment. Change in the ability to concentrate was also assessed using the PGI-C scale. The percentage of patients reporting improvement in the ability to concentrate on the PGI-C was 67% at 1 month and 70% at 6 months with AXS-12 treatment. Long-term open-label treatment with AXS-12 was also associated with improvement in overall narcolepsy status and patient functioning, assessed using the CGI-C, the PGI-C, and the Work Productivity and Activity Impairment Questionnaire, or WPAI. On the CGI-C, clinicians reported overall improvement in narcolepsy in 90% of patients at 1 month and 90% of patients at 6 months with AXS-12 treatment. Results were similar with the patient-reported PGI-C. Impairment due to narcolepsy while working was assessed after treatment with AXS-12 using the WPAI. The percentage of time impaired while working decreased substantially with AXS-12 treatment from 53% at baseline to 34% at 1 month and 24% at 6 months.

AXS-12 was well tolerated with long-term dosing, with a safety profile consistent with prior trials of AXS-12 in narcolepsy. During the 6-month open-label treatment period, the most common adverse events (≥5%) were nausea (5.9%) and tachycardia (5.9%). Over the 6-month treatment period, 17.6% of patients discontinued due to adverse events, with no individual adverse event leading to discontinuation by more than one patient. Treatment-related adverse events during the double-blind period were reported in 4.5% of patients in the AXS-12 group and 15% of patients in the placebo group. Rates of discontinuation due to adverse events in the double-blind period were 0% and 5% in the AXS-12 and placebo groups, respectively.

AXS-14

Overview

AXS-14 (esreboxetine) is a novel, oral, potent, highly selective investigational norepinephrine reuptake inhibitor being developed for the management of fibromyalgia. Esreboxetine, the SS-enantiomer of reboxetine, is more potent and selective than racemic reboxetine.

In January 2020, we received from Pfizer an exclusive license to develop and commercialize esreboxetine in the U.S. for fibromyalgia and other indications. The license encompasses nonclinical and clinical data for esreboxetine including results from a positive Phase 3 and a positive Phase 2 trial of esreboxetine in the treatment of fibromyalgia conducted by Pfizer.

Fibromyalgia

Fibromyalgia is a chronic disorder often characterized by widespread musculoskeletal pain, fatigue, disturbed sleep, depression, and cognitive impairment. Other symptoms of this disorder can include tingling in the hands and feet and headaches. Fibromyalgia is considered to be mediated mainly in the central nervous system. Approximately 17 million people in the U.S. suffer from fibromyalgia. Treatment options for fibromyalgia are limited with only three pharmacologic treatments currently approved by the FDA.

In a Phase 3 trial conducted by Pfizer in 1,122 patients with fibromyalgia treated with esreboxetine or placebo for 14 weeks, esreboxetine met the two primary endpoints by demonstrating statistically significant improvements in the weekly mean pain score compared to placebo ($p<0.001$, $p<0.001$, and $p=0.025$ for 4 mg, 8 mg and 10 mg daily doses, respectively), and the Fibromyalgia Impact Questionnaire, or FIQ, total score ($p<0.001$, $p<0.001$, and $p=0.023$ for 4 mg, 8 mg and 10 mg daily doses, respectively). Esreboxetine also resulted in statistically significant improvements in patient-reported global functioning compared to placebo as measured by the PGI-C scale ($p=0.002$, $p=0.001$, and $p=0.007$ for 4 mg, 8 mg and 10 mg daily doses, respectively), and in fatigue as measured by the Global Fatigue Index ($p=0.001$ and $p=0.001$ for 4 mg and 8 mg daily doses, respectively).

In a Phase 2 trial conducted by Pfizer in 267 patients with fibromyalgia treated with esreboxetine (dose escalated to 8 mg/day) or placebo for 8 weeks, esreboxetine met the primary endpoint by demonstrating statistically significant improvements in the weekly mean pain score compared to placebo ($p=0.006$). The study also demonstrated statistically significant improvements in additional efficacy outcomes including the FIQ total score ($p<0.001$), the PGI-C scale ($p<0.001$), and fatigue as measured by the Multidimensional Assessment of Fatigue scale ($p<0.001$).

Solriamfetol

Overview

Solriamfetol is an oral, DNRI, TAAR1 agonist, and 5-HT1A agonist being developed for the treatment of CNS disorders. We are currently developing solriamfetol in ADHD, MDD, BED, and SWD.

Attention Deficit Hyperactivity Disorder

ADHD is a chronic neurobiological and developmental disorder characterized by a persistent pattern of inattention, hyperactivity, or impulsivity that interferes with functioning or development. Impairments in cognition are apparent in attention, planning and problem solving, working memory, and behavioral inhibition. An estimated 22 million people in the U.S. are affected by ADHD, including approximately 7 million children aged 3-17 years old. Approximately two-thirds or more children with ADHD continue to have symptoms and challenges into adulthood. ADHD is associated with significant impairment in social, academic, and occupational functioning and development. The total annual societal excess costs associated with adult ADHD in the U.S. have been estimated at $122.8 billion.

FOCUS Study

In July 2023, we initiated the FOCUS study, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of solriamfetol for the treatment of ADHD in adults. Approximately 450 patients will be randomized in a 1:1:1 ratio to receive solriamfetol (150 mg or 300 mg) or placebo for 6 weeks. The primary endpoint is the change in the Adult ADHD Investigator Symptom Report Scale, or AISRS.

Major Depressive Disorder

MDD is a debilitating, chronic, biologically based disorder characterized by low mood, inability to feel pleasure, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms, which impair social, occupational, educational, or other important functioning. In severe cases, MDD can result in suicide. MDD is one of the most common mental disorders in the U.S. where approximately 1 in 5 individuals will experience MDD at some point in their life. According to the U.S. Department of Health and Human Services, or HHS, an estimated 21 million adults in the U.S. experience MDD each year. In addition, according to the World Health Organization, or WHO, depression is the leading cause of disability worldwide and is a major contributor to the overall global burden of disease. Over 70% of patients experience only a partial improvement in symptoms with first-line standard of care.

PARADIGM Study

In March 2024, we initiated the PARADIGM study, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of solriamfetol for the treatment of MDD in adults. Approximately 300 patients will be randomized in a 1:1 ratio to receive solriamfetol (300 mg) or placebo for 6 weeks. The primary endpoint is the change in the Montgomery Åsberg Depression Rating Scale, or MADRS.

Binge Eating Disorder

BED is the most common eating disorder, affecting an estimated 7 million people in the U.S. While BED is 1.75 times more common in women than men, it is still more common in men than other eating disorders. BED is thought to involve issues with food reward processing, impulse control, and appetite regulation, and is associated with a 2- to 3-fold increased risk of psychiatric or medical comorbidities. Most people with BED remain untreated with approximately one quarter of patients having received treatment in the past year and less than half receiving treatment in their lifetime. Treatment options are limited, with only one product currently approved for the treatment of BED. In November 2023, we announced that we had received from the FDA positive Pre-IND meeting written guidance on a proposed clinical developmental plan for solriamfetol in BED. In November 2023, we announced that we had received from the FDA positive Pre-IND meeting written guidance on a proposed clinical developmental plan for solriamfetol in BED.

ENGAGE Study

In April 2024, we initiated the ENGAGE study, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of solriamfetol for the treatment of BED in adults. Approximately 450 patients will be randomized in a 1:1:1 ratio to receive solriamfetol (150 or 300 mg) or placebo for 12 weeks. The primary endpoint is the change in days with binge eating episodes.

Shift Work Disorder

SWD is a combination of excessive sleepiness, or ES, during wakefulness and persistent insomnia during daytime sleep when working outside a 7 a.m. to 6 p.m. workday. An estimated 15 million working Americans may suffer from SWD, of whom 10-43% are diagnosed with SWD. Shift work has long been associated with multiple serious health complaints and a 23% greater risk of sustaining a work-related injury. Treatment options are limited, with only two products currently approved for the treatment of ES associated with SWD. In November 2023, we announced that we had received from the FDA positive Pre-IND meeting written guidance on a proposed clinical developmental plan for solriamfetol for ES associated with SWD.

SUSTAIN Study

In August 2024, we announced we had initiated the SUSTAIN study, a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of solriamfetol for the treatment of SWD in adults. Approximately 450 patients will be randomized in a 1:1:1 ratio to receive solriamfetol (150 or 300 mg) or placebo for 12 weeks. The primary endpoint is the change in the CGI-C score.

Pain and Primary Care

We continue to own and maintain the intellectual property covering our pain and primary care assets that we are not currently developing.

Commercial Agreements

We have customary clinical and commercial supply agreements and customary agreements with third-parties to help manage our clinical trials. Our commercial agreements are generally non-exclusive, and we have no material contractual obligations under such agreements, except to the extent we order supply or request services to be performed.

Material License Agreements

Exclusive License Agreement with Pfizer

In January 2020, we entered into an agreement with Pfizer for an exclusive U.S. license to Pfizer's clinical and nonclinical data, and intellectual property for reboxetine, the active pharmaceutical ingredient in AXS-12 which Axsome is developing for the treatment of narcolepsy. The agreement also provides Axsome exclusive rights to develop and commercialize esreboxetine, a new late-stage product candidate now referred to as AXS-14, in the U.S. for the treatment of fibromyalgia. Under the terms of the agreement, we received from Pfizer an exclusive U.S. license to Pfizer data for reboxetine and esreboxetine encompassing a full range of nonclinical studies, and short-term and long-term clinical trials involving more than five thousand patients. The licensed data includes results of a positive Phase 3 and a positive Phase 2 trial of esreboxetine in the treatment of fibromyalgia. we will have the exclusive right and sole responsibility of developing AXS-14 (esreboxetine) in the U.S. for the treatment of fibromyalgia and for other indications. Pfizer received 82,019 shares of our common stock having a value of $8 million, based on the average closing price of our common stock for the 10 prior trading days of $97.538, in consideration for the license and rights. Pfizer also received an upfront cash payment of $3 million and will receive up to $323 million in regulatory and sales milestones and tiered mid-single to low double-digit royalties on future sales. Pfizer will also have a right of first negotiation on any potential future strategic transactions involving AXS-12 and AXS-14. Under the agreement, we are obligated to use commercially reasonable efforts to develop, manufacture and commercialize the compounds and products in the United States and to seek and maintain regulatory approvals for the compounds and products. The agreement will expire on a product-by-product basis upon expiration of the last-to-expire royalty term for such product. On expiration (but not earlier termination), we will have a perpetual, non-exclusive, fully paid-up, royalty-free and irrevocable license under the licensed patent rights and related data to develop, manufacture, use, commercialize and otherwise exploit the compounds. Either party may terminate the agreement for the other party's material breach following a cure period. Pfizer may immediately terminate the agreement upon certain insolvency events relating to us. We may terminate the agreement for any reason upon ninety days written notice to Pfizer at any time after the first anniversary of the agreement.

Exclusive License Agreements with Antecip

In 2012, we entered into three exclusive license agreements with Antecip Bioventures II LLC, or Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board of Directors, or the Board, Herriot Tabuteau, M.D., in which we were granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the development of AXS-05 anywhere in the world for veterinary and human therapeutic and diagnostic use, and additional patents and applications that are not relevant to our current programs in development. The agreements were amended in August 2015 to update the schedule of patents and applications subject to the license agreements. Pursuant to the agreements, we are required to use commercially reasonable efforts to develop, obtain regulatory approval for, and commercialize AXS-05. Under the terms of the agreements, we are required to pay to Antecip a royalty equal to 3.0% for AXS-05, of net sales of products containing the licensed technology by us, our affiliates, or permitted sublicensees. These royalty payments are subject to reduction by an amount up to 50.0% of any required payments to third parties. Unless earlier terminated by a party for cause or by us for convenience, the agreements remain in effect on a product by product and country by country basis until the later to occur of (1) the applicable product is no longer covered by a valid claim in that country or (2) 10 years from the first commercial sale of the applicable product in that country. Upon expiration of the agreements with respect to a product in a country, our license grant for that product in that country will become a fully paid-up, royalty-free, perpetual, non-exclusive license. If Antecip terminates any of the agreements for cause, or if we exercise our right to terminate any of the agreements for convenience, the rights granted to us under such terminated agreement will revert to Antecip. Due to product sales of Auvelity since the fourth quarter of 2022, we recorded royalty expense for royalty payments due to Antecip equal to 3.0% of net sales. This is considered to be a related party transaction.

Royalty Agreement with Jazz Pharmaceuticals, SK Biopharmaceuticals Co., Ltd. and Aerial Biopharma, LLC

In connection with the Acquisition, in addition to the upfront purchase price, we assumed certain liabilities in connection with the Acquisition and agreed to make non-refundable, non-creditable royalty payments to Jazz on U.S. net sales. There are no royalty payments due to Jazz for net sales outside of the U.S. In addition, we assumed all of the commitments of Jazz to SK and Aerial Biopharma, LLC, or Aerial. The assumed commitments to SK and Aerial include single-digit tiered royalties based on the Company's sales of Sunosi, and additionally, the Company is committed to pay up to $165 million based on revenue milestones and $1 million based on development milestones. We are dependent on these agreements, and if we breach these agreements, our business, financial condition, results of operations, and prospects will be materially harmed.

Pharmanovia

In February 2023, we announced a licensing transaction with Pharmanovia to market Sunosi in Europe and certain countries in the Middle East / North Africa. Refer to Note 16. License Agreements to our consolidated financial statements included in Part IV, Exhibits and Financial Statement Schedules, of this Annual Report on Form 10-K for further detail.

Intellectual Property

We seek to protect our product candidates and our technology through a combination of patents, trade secrets, proprietary know-how, FDA and EMA exclusivity, and contractual restrictions on disclosure. Our policy is to pursue, maintain, and defend patent rights whether developed internally or licensed from third parties and to protect the proprietary position of our product candidates by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions, and improvements that are important to the development of our business. U.S. patents generally have a term of 20 years from the earliest effective date of the application.

As of February 11, 2025, our intellectual property portfolio contains more than 600 issued patents and more than 400 pending applications in the United States and worldwide. More than 140 issued United States patents and more than 91 issued foreign patents cover our AXS-05 product candidate, which has claims covering method of treatment, pharmaceutical composition, drug delivery, and pharmacokinetics, with protection extending through 2043. More than 98 issued United States patents and more than 131 issued foreign patents covering our AXS-07 product candidate, and related compounds, have claims covering various aspects, including pharmacokinetics, pharmaceutical composition, method of delivery, and methods of use with protection extending through 2040. Eight issued United States patents and two issued foreign patents covering our AXS-12 product candidate with protection extending through 2039. We have pending PCT applications, as well as pending applications in Australia, Brazil, Canada, Chile, China, Europe, Hong Kong, Israel, Japan, Mexico, Panama, Singapore, South Korea, and New Zealand. We have other patent applications with claims covering the other programs in our pipeline, including those that are not relevant to our current programs in development. As with respect to Sunosi, Orange Book listed patents in the United States extend out to 2042. We also have patents in various other countries pertaining to Sunosi.

Many pharmaceutical companies, biotechnology companies, and academic institutions are competing with us in the field of CNS disorders and filing patent applications potentially relevant to our business. In order to contend with the inevitable possibility of third-party intellectual property conflicts, from time to time we review and assess the third-party intellectual property landscape for competitive and other developments that may inform or impact our intellectual property development and commercialization strategies. With respect to third-party intellectual property, it is impossible to establish with certainty that our product candidates or discovery platform will be free of claims by third-party intellectual property holders or whether we will require licenses from such third parties. Even with modern databases and online search engines, literature searches are imperfect and may fail to identify relevant patents and published applications. Even when a third-party patent is identified, we may conclude, upon a thorough analysis, that we do not infringe the patent or that the patent is invalid. If the third-party patent owner disagrees with our conclusion and we continue with the business activity in question, we might have patent litigation forced upon us. Alternatively, we might decide to initiate litigation in an attempt to have a court declare the third-party patent invalid or not infringed by our activity. In either scenario, patent litigation typically is costly and time consuming, and the outcome is uncertain. The outcome of patent litigation is subject to uncertainties that cannot be quantified in advance, for example, the credibility of expert witnesses who may disagree on technical interpretation of scientific data. Ultimately, in the case of an adverse outcome in litigation, we could be prevented from commercializing a product or using certain aspects of our discovery platform as a result of patent infringement claims asserted against us. This could have a material adverse effect on our business. In addition to patents, we rely upon unpatented trade secrets, know how, and continuing technological innovation to develop and maintain a competitive position. We seek to protect our proprietary information, including our trade secrets and proprietary know how, by requiring our employees to execute Proprietary Information, Inventions, Non-Solicitation, and Non-Competition Agreements upon the commencement of their employment. Consultants and other advisors are required to sign consulting agreements. These agreements generally provide that all confidential information developed or made known during the course of the relationship with us be kept confidential and not be disclosed to third parties except in specific circumstances. In the case of our employees, the agreements also typically provide that all inventions resulting from work performed for us, utilizing our property, or relating to our business and conceived or completed during employment shall be our exclusive property to the extent permitted by law. Further, we require confidentiality agreements from entities that receive our confidential data or materials.

Sales and Marketing

We have built a commercial infrastructure in the United States to commercialize our products and will further expand that team as we plan for anticipated drug approvals of our product candidates. We believe that we have cost-effectively implemented a targeted sales force required to commercialize our products. Support for this team includes sales management, internal sales support, market access, distribution support, and an internal marketing group. We may seek co-promotion partners for our sales efforts to achieve broader reach or call frequency with other United States target physicians. We believe that there are significant market opportunities for our products outside of the United States. As a result, we plan to seek strategic partnerships with third parties, which may have greater reach and resources by virtue of their size and experience in the field, for the development and commercialization of our products outside the United States. We may elect in the future to utilize strategic partners, distributors, or contract sales forces to assist in the commercialization of our products. In order to implement this infrastructure, we will have to allocate management resources and make significant financial investments including some prior to product approval.

Competition

Overview

Our industry is highly competitive and subject to rapid and significant technological change. The large size and expanding scope of the CNS markets make them attractive therapeutic areas for biopharmaceutical businesses. Our competitors include pharmaceutical, biotechnology, and specialty pharmaceutical companies. While we believe that our employees and consultants, scientific knowledge, technology, and development experience provide us with competitive advantages, we face competition from many different sources, including major pharmaceutical, specialty pharmaceutical, and biotechnology companies, academic institutions and governmental agencies, and public and private research institutions. Several of these entities have robust drug pipelines, readily available capital, and established research and development organizations. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. Many of our competitors may have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical, biotechnology, and diagnostic industries may result in even more resources being concentrated among a smaller number of our competitors. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Small or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. The key competitive factors affecting the success of all of our product candidates are likely to be their efficacy, safety, convenience, price, the level of branded and generic competition, and the availability of reimbursement from government and other third party payors. Patients with MDD are typically treated with a variety of anti-depressant medications. Some of these treatments include: generic and/or branded forms of Prozac, the branded form of which is marketed by Eli Lilly and Company; Zoloft, which is marketed by Pfizer; Trintellix, which is marketed by Takeda Pharmaceuticals America, Inc. and H. Lundbeck A/S; Rexulti, which is marketed by Otsuka Pharmaceutical Co., Ltd., and Lundbeck A/S; Vraylar and Viibryd, which are marketed by AbbVie; Effexor, which is marketed by Pfizer; and Wellbutrin, which is marketed by GlaxoSmithKline. We are aware of several companies developing compounds for the treatment of depression, including Xenon Pharmaceuticals, Inc., Neumora Therapeutics, Inc., Johnson & Johnson, Otsuka Pharmaceutical Co. Ltd., Neurocrine Biosciences, Inc., Intra-Cellular Therapies, Inc., and Biohaven Ltd. Patients with EDS have available to them a variety of medications, such as generic and/or branded forms of Xyrem and Xywav, which are marketed by Jazz; Wakix, which is marketed by Harmony Biosciences LLC; Lumryz, which is marketed by Avadel Pharmaceuticals plc; Provigil and Nuvigil, which are manufactured by Teva Pharmaceutical Industries Limited, or Teva.

CNS Product Candidates

AXS-05 Competition

We are aware of other companies working to develop therapeutics for the treatment of agitation associated with AD, including Otsuka Pharmaceutical Co. Ltd., which is working to develop a combination of deuterated dextromethorphan and quinidine, and Otsuka and Lundbeck A/S, which recently received approval for Rexulti for this indication. Products approved for smoking cessation include Chantix, which is marketed by Pfizer; Zyban, which is marketed by GlaxoSmithKline; and various nicotine replacement therapies, including skin patches, chewing gums, and lozenges. We are aware of several companies developing compounds for AD agitation, including Bristol-Myers Squibb Co., BioXcel Therapeutics, Inc., Neumora Therapeutics, Inc., and Intra-Cellular Therapies, Inc.

AXS-07 Competition

There are a number of products approved for the acute treatment of migraine, including generic and/or branded forms of Maxalt, the branded form of which is marketed by Merck & Co., Inc., generic and/or branded forms of Treximet, the branded form of which is marketed by Pernix Therapeutics Holdings, Inc., Reyvow, which is marketed by Eli Lilly and Company; Nurtec, which is marketed by Pfizer, and Ubrelvy, which is marketed by AbbVie, and Trudhesa which is marketed by Impel. We are aware of several companies developing compounds for migraine, including Biohaven Ltd., Kallyope, Inc., and Lundbeck A/S.

AXS-12 Competition

Products approved to treat the symptoms of narcolepsy include generic and/or branded forms of Ritalin, the branded form of which is marketed by Novartis Pharmaceuticals; Provigil and Nuvigil, which are both marketed by Teva; Xyrem and Xywav, which are both marketed by Jazz; and Wakix which is marketed by Harmony Biosciences LLC. We are aware of several companies developing compounds for the treatment of the symptoms of narcolepsy, including Takeda Pharmaceuticals Company, Centessa Pharmaceuticals plc, Harmony Biosciences LLC, Eisai Co., Ltd., and Alkermes plc.

AXS-14 Competition

Products approved to treat fibromyalgia include generic and/or branded forms of Cymbalta, the branded form of which is marketed by Eli Lilly and Company; Lyrica, which is marketed by Pfizer; and Savella, which is marketed by AbbVie. We are aware of other companies working to develop therapeutics for the treatment of fibromyalgia, including Dogwood Therapeutics, Inc. and Tonix Pharmaceutical Holding Corp.

Manufacturing

Manufacturing of the drug substance and drug product for our products and product candidates are done by third parties and must comply with FDA current Good Manufacturing Practice, or cGMP, regulations. Our products and product candidates are comprised of synthetic small molecules made through a series of organic chemistry steps starting with commercially available organic chemical raw materials. We do not currently own or operate any manufacturing facilities for the clinical or commercial production of our drug candidates. We believe that our existing suppliers of our product and product candidate active pharmaceutical ingredients and finished products will be capable of providing sufficient quantities of each to meet our commercial and clinical trial supply needs. We conduct periodic quality audits of their facilities. Other contract manufacturing organization, or CMOs, may be used in the future for clinical supplies and/or commercial manufacturing.

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state, and local level, and in other countries and supranational regions, extensively regulate, among other things, the research, development, testing, manufacture, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, adverse event reporting and pharmacovigilance, marketing, import, and export of pharmaceutical products, such as those we are developing and for which we are seeking FDA approval. In addition, healthcare regulatory bodies in the United States and around the world impose a range of requirements related to the payment for pharmaceutical products, including laws intended to prevent fraud, waste, and abuse of healthcare dollars. This includes, for example, requirements that manufacturers of pharmaceutical products participating in Medicaid and Medicare comply with mandatory price reporting, discount, rebate requirements, and other cost control measures, as well as anti-kickback laws and laws prohibiting false claims. Some states also have enacted fraud, waste, and abuse laws that parallel (and in some cases apply more broadly than) federal laws, and in some cases price transparency requirements. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources. Further, healthcare is an active area of governmental scrutiny, and it is reasonable to expect that the requirements may become more stringent within the foreseeable future.

FDA Regulation

In the United States, the FDA regulates drugs under the FDCA and its implementing regulations. The process required by the FDA before product candidates may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies, and formulation studies in compliance with the FDA's Good Laboratory Practice, or GLP, regulations;

- submission to the FDA of an IND which must become effective before human clinical trials may begin;

- approval by an independent Institutional Review Board, or IRB, for each clinical site or centrally, before each trial may be initiated;

- adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug candidates for its intended use, performed in accordance with current Good Clinical Practices, or GCP;

- development of manufacturing processes in compliance with cGMPs to ensure the drug's identity, strength, quality, and purity;

- compilation of required information and submission to the FDA of an NDA;

- satisfactory completion of an FDA advisory committee review, if applicable;

- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMPs, and to assure that the facilities, methods, and controls are adequate to preserve the drug's identity, strength, quality, and purity, as well as satisfactory completion of an FDA inspection of selected clinical sites and selected clinical investigators to determine GCP compliance; and

- FDA review and approval of the NDA to permit commercial marketing for particular indications for use.

Preclinical Studies and IND Submission

The testing and approval process of product candidates requires substantial time, effort, and financial resources. Preclinical studies include laboratory evaluation of drug substance chemistry, pharmacology, toxicity, and drug product formulation, as well as animal studies to assess potential safety and efficacy. Such studies must generally be conducted in accordance with the FDA's GLP regulations. Prior to commencing the first clinical trial with a product candidate, an IND sponsor must submit the results of the preclinical tests and preclinical literature, together with manufacturing information, analytical data, any available clinical data or literature, and proposed clinical study protocols, among other things, to the FDA as part of an IND. In the case of 505(b)(2) applications, though, some of the IND components may not be required (for example, if previously established for an approved drug which is referenced). Some preclinical testing may continue even after the IND is submitted.

An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, notifies the applicant of safety concerns or questions related to one or more proposed clinical trials and places the trial on a clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. Clinical holds also may be imposed by the FDA at any time before or during trials due to safety concerns or noncompliance. As a result, submission of an IND may not result in FDA authorization to commence a clinical trial.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirements that all research subjects provide their informed consent in writing for their participation in any clinical trial, as well as review and approval of the study by an IRB. Investigators must also provide certain information to the clinical trial sponsors to allow the sponsors to make certain financial disclosures to the FDA. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the trial procedures, the parameters to be used in monitoring safety, the effectiveness criteria to be evaluated, and a statistical analysis plan. A protocol for each clinical trial, and any subsequent protocol amendments, must be submitted to the FDA as part of the IND. In addition, an IRB at each study site participating in the clinical trial or a central IRB must review and approve the plan for any clinical trial, informed consent forms, and communications to study subjects before a study commences at that site. An IRB considers, among other things, whether the risks to individuals participating in the trials are minimized and are reasonable in relation to anticipated benefits and whether the planned human subject protections are adequate. The IRB must continue to oversee the clinical trial while it is being conducted. Once an IND is in effect, each new clinical protocol and any amendments to the protocol must be submitted to the IND for FDA review, and to the IRB for approval. Progress reports detailing the results of the clinical trials must also be submitted at least annually to the FDA and the IRB and more frequently if serious adverse events or other significant safety information is found.

Information about certain clinical trials, including a description of the study and study results, must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their clinicaltrials.gov website.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group regularly reviews accumulated data and advises the study sponsor regarding the continuing safety of trial subjects, enrollment of potential trial subjects, and the continuing validity and scientific merit of the clinical trial. The data safety monitoring board receives special access to unblinded data during the clinical trial and may advise the sponsor to halt the clinical trial if it determines there is an unacceptable safety risk for subjects or on other grounds, such as no demonstration of efficacy.

The manufacture of investigational drugs for the conduct of human clinical trials (and their active pharmaceutical ingredients) is subject to cGMP requirements. Investigational drugs and active pharmaceutical ingredients imported into the United States are also subject to regulation by the FDA relating to their labeling and distribution. Further, the export of investigational drug products outside of the United States is subject to regulatory requirements of the receiving country as well as U.S. export requirements under the FDCA.

In general, for purposes of NDA approval, human clinical trials are typically conducted in three sequential phases, which may overlap or be combined.

- *Phase 1*—Studies are initially conducted in healthy human volunteers or subjects with the target disease or condition and test the product candidate for safety, dosage tolerance, structure-activity relationships, mechanism of action, absorption, metabolism, distribution, and excretion. If possible, Phase 1 trials may also be used to gain an initial indication of product effectiveness.

- *Phase 2*—Controlled studies are conducted in limited subject populations with a specified disease or condition to evaluate preliminary efficacy, identify optimal dosages, dosage tolerance and schedule, possible adverse effects and safety risks, and expanded evidence of safety.

- *Phase 3*—These adequate and well-controlled clinical trials are undertaken in expanded subject populations, generally at geographically dispersed clinical trial sites, to generate enough data to provide statistically significant evidence of clinical efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product, and to provide adequate information for the labeling of the product. Typically, two Phase 3 trials are required by the FDA for product approval.

The FDA may also require, or companies may conduct, additional clinical trials for the same indication after a product is approved. These so-called Phase 4 studies may be required by the FDA as a condition of approval of the NDA, to be satisfied after approval. The results of Phase 4 studies can confirm the effectiveness of a product candidate and can provide important safety information. In addition to the above traditional kinds of clinical trial data required for the approval of an NDA, the 21st Century Cures Act provides for potential FDA use of different types and sources of data in regulatory decision-making, such as patient experience data, real world evidence for already approved products, and, for appropriate indications sought through supplemental marketing applications, data summaries. Implementation of this law and related initiatives is still in progress and we do not know the extent to which we may in the future be able to utilize these types and sources of data. In the case of a 505(b)(2) NDA, which is a marketing application in which sponsors may rely on investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted, some of the above described studies and preclinical studies may not be required or may be abbreviated. Bridging studies may be needed, however, to demonstrate the applicability of the studies that were previously conducted by other sponsors to the drug that is the subject of the marketing application.

Clinical trials at any phase may not be completed successfully within any specified period, or at all. Regulatory authorities, an IRB, or the sponsor may suspend or discontinue a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk, the clinical trial is not being conducted in accordance with the FDA's or the IRB's requirements, if the drug has been associated with unexpected serious harm to the subjects, or based on evolving business objectives or competitive climate.

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product candidate as well as finalize a process for manufacturing the product 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, the manufacturer must develop methods for testing the identity, strength, quality, potency, and purity of the final product. Additionally, 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.

During the development of a new drug, a sponsor may be able to request a SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 clinical trial protocol design and analysis that will form the primary basis of an efficacy claim as well as preclinical carcinogenicity trials and stability studies. An SPA may only be modified with the agreement of the FDA and the trial sponsor or if the director of the FDA reviewing division determines that a substantial scientific issue essential to determining the safety or efficacy of the drug was identified after the testing began. An SPA is intended to provide assurance that, in the case of clinical trials, if the agreed upon clinical trial protocol is followed, the clinical trial endpoints are achieved, and there is a favorable risk benefit profile, the data may serve as the primary basis for an efficacy claim in support of an NDA. However, SPA agreements are not a guarantee of an approval of a product candidate or any permissible claims about the product candidate. In particular, SPAs are not binding on the FDA if, among other reasons, previously unrecognized public health concerns arise during the performance of the clinical trial, other new scientific concerns regarding the product candidate's safety or efficacy arise, or if the sponsoring company fails to comply with the agreed upon clinical trial protocol.

NDA Submission, Review by the FDA, and Marketing Approval

Assuming successful completion of the required clinical and preclinical testing, the results of product development, including CMC information, non-clinical studies, and clinical trial results, including negative or ambiguous results as well as positive findings, are all submitted to the FDA, along with the proposed labeling, as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee, authorized every five years by Congress under PDUFA. User fees must be paid at the time of the first submission of the application, even if the application is being submitted on a rolling basis, and, if approved, program fees must be paid on an annual basis. Product candidates that are designated as orphan drugs, which are further described below, are also not subject to application user fees unless the application includes an indication other than the orphan indication.

In addition, under the Pediatric Research Equity Act, or PREA, an NDA or supplement to an NDA for a new active ingredient, indication, dosage form, dosage regimen, or route of administration must contain data that are adequate to assess the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. A sponsor who is planning to submit a marketing application for a drug product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration must submit an initial Pediatric Study Plan, or PSP, within 60 days of an End-of-Phase 2 meeting or as may be agreed between the sponsor and the FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach agreement on the PSP. A 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 preclinical studies, early phase clinical studies or other clinical development programs. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, to ensure that the benefits of the drug outweigh the risks of the drug. The REMS plan could include medication guides, physician communication plans, and elements to assure safe use, such as restricted distribution methods, patient registries, or other risk minimization tools. An assessment of the REMS must also be conducted at set intervals. Following product approval, a REMS may also be required by the FDA if new safety information is discovered, and the FDA determines that a REMS is necessary to ensure that the benefits of the drug continue to outweigh the risks of the drug.

Once the FDA receives an application, it will determine within 60 days whether the NDA as filed is sufficiently complete to permit a substantive review (with this decision often referred to as the NDA being "accepted for filing"). The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the NDA.

The FDA has agreed to a set of performance goals and procedures under PDUFA to review 90% of all applications within ten months from the 60-day filing date for its initial review of a standard NDA for a New Molecular Entity, or NME. For non-NME standard applications, the FDA has set the goal of completing its review of 90% of all applications within ten months from the submission receipt date. Such deadlines are referred to as the PDUFA date. The PDUFA date is only a goal, thus, the FDA does not always meet its PDUFA goal dates. The review process and the PDUFA goal date may also be extended if the FDA requests, or the NDA sponsor otherwise provides, substantial additional information or clarification regarding the submission.

The FDA may refer an application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved, and applications for new molecular entities are generally discussed at advisory committee meetings unless the FDA determines that this type of consultation is not needed under the circumstances.

An advisory committee is typically a panel that includes clinicians and other experts, which review, evaluate, and make a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions and typically follows such recommendations.

The FDA reviews applications to determine, among other things, whether a product is safe and effective for its intended use and whether the manufacturing methods and controls are adequate to assure and preserve the product's identity, strength, quality, safety, potency, and purity. Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured, referred to as a Pre-Approval Inspection. The FDA will not approve an application unless it determines that the manufacturing processes and facilities, including contract manufacturers and subcontractors, are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will inspect one or more clinical trial sites to assure compliance with GCPs.

The approval process is lengthy and difficult and involves numerous FDA personnel assigned to review different aspects of the NDA, and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional preclinical or clinical CMC, or other data and information. Uncertainties can be presented by reviewers' ability to exercise judgment and discretion during the review process. Even if such data and information are submitted, the FDA may ultimately 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 an applicant interprets the same data.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a CRL. If a CRL is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter; withdraw the application; or request an opportunity for a hearing. A CRL indicates that the review cycle of the application is complete, and the application is not ready for approval in its current form and describes all of the specific deficiencies that the FDA identified in the NDA. A CRL generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for the FDA to reconsider the application. The deficiencies identified may be minor, for example, requiring labeling changes; or major, for example, requiring additional clinical trials. The FDA has the goal of reviewing 90% of application and efficacy supplement resubmissions in either two or six months (from receipt) for a Class 1 or Class 2 resubmission, respectively. For non-efficacy supplements (i.e., labeling and manufacturing supplements), CDER's goal is to review the supplement within the same length of time (from receipt) as the initial review cycle (excluding an extension caused by a major amendment of the initial supplement).

Even with the submission of additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when the issues identified in a CRL have been addressed and resolved to the FDA's satisfaction, the FDA may issue an approval letter. An approval letter authorizes commercial marketing of the drug for specific indications and with specific prescribing information, which was reviewed in connection with the NDA.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings, or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety and efficacy after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may also not approve label statements that are necessary for successful commercialization and marketing.

After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval. The FDA may also withdraw the product approval if compliance with the pre- and post-marketing regulatory standards are not maintained or if problems occur after the product reaches the marketplace. Further, should new safety information arise, additional testing, product labeling, or FDA notification may be required.

505(b)(2) Approval Process

Section 505(b)(2) of the FDCA provides an alternate regulatory pathway to FDA approval for new or improved formulations or new uses of previously approved drug products. Specifically, Section 505(b)(2) was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act amendments, and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. The applicant may rely, in part, upon the FDA's prior findings of safety and effectiveness for an approved product that acts as the reference listed drug or on published scientific literature, in support of its application. The FDA may also require 505(b)(2) applicants to perform additional studies or measurements to support the changes from the reference listed drug as well as bridging studies to the reference listed drug. The FDA may then approve the new product candidate for all or some of the labeled indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Orange Book Listing

Section 505 of the FDCA describes three types of marketing applications that may be submitted to the FDA to request marketing authorization for a new drug. A section 505(b)(1) NDA is an application that contains full reports of investigations of safety and efficacy. A section 505(b)(2) NDA is an application in which the applicant, in part, relies on investigations that were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. Section 505(j) establishes an abbreviated approval process for a generic version of approved drug products through the submission of an ANDA. An ANDA is an application for marketing of a generic drug product that has the same active ingredients, dosage form, strength, route of administration, labeling, performance characteristics, and intended use, among other things, to a previously approved product. Limited changes must be pre-approved by the FDA via a suitability petition. ANDAs are termed "abbreviated" because they are generally not required to include preclinical and clinical data to establish safety and efficacy. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent to, or performs in the same manner as, the innovator drug through in vitro, in vivo, or other testing. The generic version must deliver the same amount of active ingredients into a subject's bloodstream in the same amount of time as the innovator drug and, under state substitution laws, may be substituted at the pharmacy for the reference listed drug.

In seeking approval for a drug through an NDA, including a 505(b)(2) NDA, applicants are required to identify to the FDA patents that contain claims that are directed to the applicant's product and/or method(s) of use. Upon approval of an NDA, each of the identified patents is then listed in *Approved Drug Products with Therapeutic Equivalence Evaluations*, also known as the Orange Book.

An applicant who files an ANDA seeking approval of a generic version of a drug listed in the Orange Book or a 505(b)(2) NDA referencing a drug listed in the Orange Book must make patent certifications to the FDA that (1) no patent information on the drug or method of use that is the subject of the application has been submitted to the FDA; (2) the patent has expired; (3) the date on which the patent has expired and approval will not be sought until after the patent expiration; or (4) in the applicant's opinion and to the best of its knowledge, the patent is invalid, unenforceable, or will not be infringed upon by the manufacture, use, or sale of the drug product for which the application is submitted. The last certification is known as a paragraph IV certification. Generally, the ANDA or 505(b)(2) NDA approval cannot be made effective until all listed patents have expired, except where the ANDA or 505(b)(2) NDA applicant challenges a listed patent through a paragraph IV certification or if the applicant is not seeking approval of a patented method of use. If the applicant does not challenge the listed patents or does not indicate that it is not seeking approval of a patented method of use, the ANDA or 505(b)(2) NDA application approval will not be made effective until all of the listed patents claiming the referenced product have expired.

If the competitor has provided a paragraph IV certification to the FDA, the competitor must also send notice of the paragraph IV certification to the holder of the NDA for the reference listed drug and the patent owner within 20 days after 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 the notice of the paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a paragraph IV certification notice prevents the FDA from making the approval of the ANDA or 505(b)(2) application effective until the earlier of 30 months from the date of the lawsuit, expiration of the patent, settlement of the lawsuit, a decision in the infringement case that is favorable to the applicant or such shorter or longer period as may be ordered by a court. This prohibition is generally referred to as the automatic 30-month stay.

In practice, where an ANDA or 505(b)(2) NDA applicant files a paragraph IV certification, the NDA holder or patent owners often take action to trigger the automatic 30-month stay, resulting in patent litigation that may take many months or years to resolve. Thus, approval of an ANDA or 505(b)(2) application could be delayed for a significant period of time depending on the patent certification the applicant makes and the reference drug sponsor's decision to initiate patent litigation.

Regulatory Exclusivity

Regulatory exclusivity provisions under the FDCA can also delay the submission or the approval effective date of certain applications. A regulatory exclusivity period can provide the holder of an approved NDA protection from new competition in the marketplace for the innovation represented by its approved drug. Five years of exclusivity are available for New Chemical Entities, or NCEs. An NCE is a drug that contains no active moiety that has been approved by the FDA in any other NDA. An active moiety is the molecule or ion excluding those appended portions of the molecule that cause the drug to be an ester, salt, including a salt with hydrogen or coordination bonds, or other noncovalent derivatives, such as a complex, chelate, or clathrate, of the molecule, responsible for the therapeutic activity of the drug substance. During the NCE exclusivity period, the FDA may not accept for review an ANDA or a 505(b)(2) NDA application by another company that contains the previously approved active moiety. An ANDA or 505(b)(2) application, however, may be submitted one year before NCE exclusivity expires if a paragraph IV certification is filed.

Three years of exclusivity are available to the holder of an NDA, including a 505(b)(2) NDA, for a particular condition of approval, or change to a marketed product, such as a new formulation or indication for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations, other than bioavailability studies, conducted by the sponsor that were essential to approval of the application. Changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration or conditions of use may be granted this exclusivity if a new clinical investigation, or NCI, was essential to approval of the application containing those changes. During the NCI exclusivity period, the FDA may not approve an ANDA or 505(b)(2) NDA by another company for the condition of the new drug's approval. NCE and NCI exclusivities 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 preclinical studies and adequate and well controlled clinical trials necessary to demonstrate safety and efficacy.

Pediatric exclusivity is a regulatory exclusivity in the United States that provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory and statutory exclusivity, including the non-patent exclusivity periods described above as well as applicable patent terms. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studies; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the required time frames, whatever statutory or regulatory periods of exclusivity or Orange Book listed patent protection cover the drug are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot make an ANDA or 505(b)(2) application approval effective as a result of regulatory exclusivity for listed patents. Moreover, pediatric exclusivity attaches to all formulations, dosage forms, and indications for products with existing marketing exclusivity or patent life that contain the same active moiety as that which was studied.

The Orphan Drug Act provides incentives for the development of drugs intended to treat rare diseases or conditions, which generally are diseases or conditions affecting less than 200,000 individuals annually in the United States, or affecting more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making the drug available in the United States will be recovered from United States sales. If a product receives FDA approval for the indication for which it has orphan designation, the product is generally entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity. Orphan Drug Designation also entitles a party to financial incentives, such as opportunities for grant funding towards clinical study costs, tax advantages, and application user-fee waivers.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including Fast Track designation, Priority Review and Breakthrough designation, which are intended to expedite or simplify the process for the development and FDA review of certain drug products that are intended for the treatment of serious or life-threatening diseases or conditions, and demonstrate the potential to address unmet medical needs or present a significant improvement over existing therapy. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a Fast Track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need. The FDA will determine that a product will fill an unmet medical need if the product will provide a therapy where none exist or provide a therapy that may be potentially superior to existing therapy based on efficacy, safety, or public health factors. If Fast Track designation is obtained, drug sponsors may be eligible for more frequent development meetings and correspondence with the FDA.

In addition, if an applicant obtains "rolling review," the FDA may accept and initiate review of sections of an NDA before the application submission is complete, although it is not guaranteed that the FDA will commence review before the application submission is complete, and the timing of the review depends on a number of factors, including availability of review personnel at the FDA and competing agency priorities, among other things. The applicant must provide, and the FDA must agree, to a schedule for the remaining information after the initial section of the NDA.

In some cases, a Fast Track product may be eligible for Accelerated Approval or Priority Review. The FDA may give a Priority Review designation to drugs that are intended to treat serious conditions and, if approved, would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions. A Priority Review designation means that the goal for the FDA is to review an application within six months of receipt, rather than the standard review of ten months under current PDUFA guidelines, of the 60-day filing date for NMEs and within six months of the submission receipt date for non-NMEs. Products that are eligible for Fast Track designation may also be considered appropriate to receive a Priority Review.

Moreover, under the provisions of the Food and Drug Administration Safety and Innovation Act, or FDASIA, enacted in 2012, a sponsor can request designation of a product candidate as a "breakthrough therapy." A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs designated as breakthrough therapies are eligible for the Fast Track designation features as described above, intensive guidance on an efficient drug development program beginning as early as Phase 1 trials, and a commitment from the FDA to involve senior managers and experienced review staff in a proactive collaborative, and cross-disciplinary review.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Post-approval Requirements

Any product manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, as well as other federal and state agencies, including, among other things, requirements related to manufacturing, recordkeeping, and reporting, including adverse experience reporting, drug shortage reporting, and other periodic reporting; drug supply chain security surveillance and tracking requirements; product sampling and distribution; advertising; marketing; promotion; certain electronic records and signatures; licensure in certain states for the manufacturing and distribution of drug products; and post-approval obligations imposed as a condition of approval, such as Phase 4 clinical trials, REMS, and surveillance to assess safety and effectiveness after commercialization.

After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There are also continuing annual prescription drug program user fee requirements for any approved products. In addition, 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 list their drug products, and are subject to periodic announced and unannounced inspections by the FDA and these state agencies for compliance with cGMP and other requirements, which impose certain procedural and documentation requirements upon the company and third-party manufacturers.

Changes to the manufacturing process are strictly regulated and often require prior FDA approval or notification before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and specifications and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

The FDA also strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. A company can make only those claims relating to safety and efficacy, purity, and potency that are approved by the FDA. Physicians, in their independent professional medical judgment, may prescribe legally available products for unapproved indications that are not described in the product's labeling and that differ from those tested and approved by the FDA. Pharmaceutical companies, however, are required to promote their drug products only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off label uses, and a company that is found to have improperly promoted off label uses may be subject to significant liability, including, but not limited to, criminal and civil penalties under the FDCA and False Claims Act, or FCA, exclusion from participation in federal healthcare programs, mandatory compliance programs under corporate integrity agreements, debarment, and refusal of government contracts. Recent court decisions have impacted the FDA's enforcement activity regarding off-label promotion in light of First Amendment considerations; however, there are still significant risks in this area in part due to the potential FCA exposure. Further, the FDA has not materially changed its position on off-label promotion following legal setbacks on First Amendment grounds and the DOJ has consistently asserted in FCA briefings that "speech that serves as a conduit for violations of the law is not constitutionally protected."

Commercial products must meet the requirements of the Drug Supply Chain Security Act, or DSCSA, which imposes obligations on manufacturers of prescription biopharmaceutical products for commercial distribution, regulates the distribution of the products at the federal level, and sets certain standards for federal or state registration and compliance of entities in the supply chain (manufacturers and repackagers, wholesale distributors, third-party logistics providers, and dispensers). The DSCSA preempts certain previously enacted state pedigree laws and the pedigree requirements of the Prescription Drug Marketing Act, or PDMA. Trading partners within the drug supply chain must now ensure they are meeting certain product tracing requirements; they are doing business with other authorized trading partners; and they are exchanging transaction information, transaction history, and transaction statements. Product identifier information (an aspect of the product tracing scheme) is also now required. The DSCSA requirements, development of standards, and the system for product tracing have been and will continue to be phased in over a period of years, with the FDA indicating enforcement discretion on certain aspects due to the COVID-19 pandemic. The distribution of product samples continues to be regulated under the PDMA, and some states also impose regulations on drug sample distribution.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in significant regulatory actions. Such actions may include refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, imposition of a clinical hold or termination of clinical trials, warning letters, untitled letters, modification of promotional materials or labeling, provision of corrective information, imposition of post market requirements, including the need for additional testing, imposition of distribution or other restrictions under a REMS, product recalls, product seizures or detentions, refusal to allow imports or exports, total or partial suspension of production or distribution, FDA debarment, injunctions, fines, consent decrees, corporate integrity agreements, debarment from receiving government contracts and new orders under existing contracts, exclusion from participation in federal and state healthcare programs, restitution, disgorgement, or civil or criminal penalties, including fines and imprisonment, and may result in adverse publicity, among other adverse consequences.

Fraud and Abuse, and Transparency Laws and Regulations

Our business activities, including but not limited to, research, sales, promotion, marketing, distribution, medical education, sponsorships, relationships with prescribers and other referral sources, are subject to regulation by numerous federal and state regulatory and law enforcement authorities in the United States in addition to the FDA, including potentially the Department of Justice, HHS and its various divisions, including the Centers for Medicare & Medicaid Services, or CMS, the Office of Inspector General, or OIG, and the Health Resources and Services Administration, or HRSA, the Department of Veterans Affairs, the Department of Defense, and certain state and local governments. Our business activities must comply with numerous healthcare laws, including but not limited to, anti-kickback and false claims laws and regulations as well as data privacy and security laws and regulations, which are described below.

The federal Anti-Kickback Statute prohibits, among other things, any person or entity from knowingly and willfully offering, paying, soliciting, or receiving any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or in return for purchasing, leasing, ordering, or arranging for or recommending the purchase, lease, furnishing, or order of any item or service reimbursable under Medicare, Medicaid, or other federal healthcare programs, in whole or in part. The term "remuneration" has been interpreted broadly to include anything of value. The Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, formulary managers, and beneficiaries on the other. There are certain statutory exceptions and regulatory safe harbors protecting some common activities from prosecution. The exceptions and safe harbors are drawn narrowly, and practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases, or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor, however, does not make the conduct per se illegal under the Anti-Kickback Statute. The safe harbors are subject to change through legislative and regulatory action, and we may decide to adjust our business practices or be subject to heightened scrutiny as a result. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances to determine whether one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered businesses. Additionally, the intent standard under the Anti-Kickback Statute provides that a person or entity need not have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, 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 federal civil FCA. Therefore, either the federal government or private citizens under the FCA's qui tam provisions (discussed further below) can bring an action under the FCA for violations of the Anti-Kickback Statute, potentially exposing an alleged violator to substantial monetary damages and penalties. Certain Anti-Kickback safe harbor provisions that protect the rebates paid by drug manufacturers to third parties may also be repealed or materially revised, as contemplated in a recent regulatory proposal.

The government has asserted FCA liability against manufacturers by alleging that improper arrangements with ordering physicians caused them or another provider to file false claims in violation of the FCA or that manufacturers' support of patient assistance programs improperly induced beneficiaries to choose their products in violation of the Anti-Kickback Statute. Sales, marketing and business arrangements in the healthcare industry are also 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, patient assistance programs, and other business arrangements. Medicare Advantage and Medicaid managed care plan regulations prohibit certain forms of marketing to enrollees that are designed to discriminate against beneficiaries on the basis of their health conditions or history. These regulations may require regulatory review of marketing materials, and coordination with health plan or governmental regulators. Additionally, the federal government has pursued electronic health record, or EHR, vendors and pharmaceutical manufacturers for remunerative relationships involving the EHR platform's recommendation of particular drugs and "prompting" technology to increase prescribing of particular drugs.

The Physician Payments Sunshine Act, or the Sunshine Act, requires applicable manufacturers of covered drugs for which payment is available under Medicare, Medicaid, or the State Children's Health Insurance Program, among others, to track and report annually to the federal government (for disclosure to the public) certain payments and other transfers of value they make to physicians, teaching hospitals, physician assistants, nurse practitioners, and other mid-level practitioners. We are also required to report certain ownership and investment interests held by physicians and their immediate family members.

The federal civil FCA prohibits, among other things, any person or entity from knowingly presenting, or causing to be presented, a false or fraudulent claim for payment to, or approval by, the federal government, knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government, or avoiding, decreasing, or concealing an obligation to pay money to the federal government. A claim includes "any request or demand" for money or property presented directly or indirectly to the U.S. government. The civil FCA has been used to assert liability on the basis of kickbacks and other improper referrals, improperly reported government pricing metrics, such as Best Price or Average Manufacturer Price, or submission of inaccurate information required by government contracts, improper use of Medicare provider or supplier numbers when detailing a provider of services, improper promotion of off-label uses not expressly approved by the FDA in a drug's label, and allegations as to misrepresentations with respect to the products supplied or services rendered. Several pharmaceutical and other healthcare companies have further been sued under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Civil FCA actions may be brought by the government or may be brought by private individuals on behalf of the government, called "qui tam" actions. If the government decides to intervene in a qui tam action and prevails in the lawsuit, the individual will share in the proceeds from any fines or settlement funds. If the government declines to intervene, the individual may pursue the case alone, subject to governmental review and certain approvals. Qui tam complaints are filed under seal, and the cases may progress for a number of years before a complaint is unsealed and a manufacturer becomes aware of its existence. Since 2004, these FCA lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements, as much as $3.0 billion, regarding certain sales practices and promoting off-label drug uses. For example, civil FCA liability may be imposed for Medicare or Medicaid overpayments arising out of claims that were filed by providers but alleged to have been caused by manufacturers' incentives, impermissible discounts, or overpayments caused by understated rebate amounts. FCA enforcement may also arise from claims filed as the result of manufacturing marketing materials that contained inaccurate statements or provided certain reimbursement guidance.

The government may further prosecute conduct constituting a false claim under the criminal FCA. The criminal FCA prohibits the making or presenting of a claim to the government knowing such claim to be false, fictitious, or fraudulent and, unlike the civil FCA, requires proof of intent to submit a false claim. Similarly, the criminal healthcare fraud statutes impose criminal liability for, among other things, knowingly and willfully attempting or executing a scheme to defraud any healthcare benefit program, including private third-party payors, obtaining money or property of a benefit program by false or fraudulent means, or falsifying, concealing, or covering up a material fact or submitting a materially false statement in connection with the delivery of, or payment from healthcare benefits, items, or services. These statutes are not limited to items and services reimbursed by a governmental health care program and have been used to prosecute commercial insurance fraud as well.

The federal Civil Monetary Penalties Law authorizes the imposition of substantial civil monetary penalties against an entity, such as a pharmaceutical manufacturer, that engages in activities including, among others: (1) knowingly presenting, or causing to be presented, a claim for services not provided as claimed or that is otherwise false or fraudulent in any way; (2) arranging for or contracting with an individual or entity that is excluded from participation in federal healthcare programs to provide items or services reimbursable by a federal healthcare program; (3) violations of the federal Anti-Kickback Statute; or (4) failing to report and return a known overpayment.

The exclusion statute requires the exclusion of entities and individuals who have been convicted of federal-program related crimes or health care felony fraud or controlled substance charges. The statute also permits the exclusion of those that have been convicted of any form of fraud, the Anti-Kickback Statute, for obstructing an investigation or audit, misdemeanor-controlled substance charges, those whose health care license has been revoked or suspended, and those who have filed claims for excessive charges or unnecessary services. If a company were to be excluded, its products would be ineligible for reimbursement from any federal programs, including Medicare and Medicaid, and no other entity participating in those programs would be permitted to enter into contracts with the company. Further, employment or contracting with an individual or entity that has been excluded from participation in federal healthcare programs could serve as a basis to invalidate claims for items or services submitted by that entity and to exclude that entity from participation in such programs as well. In order to preserve access to beneficial drugs, the government may elect to exclude officers and key employees of manufacturers, rather than excluding the organization. Such enforcement actions would prohibit the Company from engaging those individuals, which could adversely affect operations, and could result in significant reputational harm.

The compliance and enforcement landscape, and related risk, is informed by government litigation and settlement precedent, Advisory Opinions, and Special Fraud Alerts. Our approach to compliance may evolve over time in light of these types of developments.

Payment or reimbursement of prescription drugs by Medicaid or Medicare requires manufacturers of the drugs to submit pricing information to CMS. The Medicaid Drug Rebate statute requires manufacturers to calculate and report price points, which are used to determine Medicaid rebate payments shared between the states and the federal government and Medicaid payment rates for certain drugs. For drugs paid under Medicare Part B, manufacturers must also calculate and report their Average Sales Price, which is used to determine the Medicare Part B payment rate for the drug. Drugs that are approved under a Biologic License Application, or BLA, or an NDA, including 505(b)(2) drugs, are subject to an additional inflation penalty, which can substantially increase rebate payments. In addition, for BLA and NDA drugs, the Veterans Health Care Act, or VHCA, requires manufacturers to calculate and report to the Veterans Administration, or VA, a different price called the Non Federal Average Manufacturing Price, which is used to determine the maximum price that can be charged to certain federal agencies, referred to as the Federal Ceiling Price, or FCP. Like the Medicaid rebate amount, the FCP includes an inflation penalty. A Department of Defense regulation requires manufacturers to provide this discount through prescription rebates on drugs dispensed by retail pharmacies when paid by the TRICARE Program. All of these price reporting requirements create risk of submitting false information to the government and resulting potential FCA liability.

The VHCA also requires manufacturers of covered drugs participating in the Medicaid program to enter into Federal Supply Schedule contracts with the VA through which their covered drugs must be sold to certain federal agencies at FCP and to report pricing information. This necessitates compliance with applicable federal procurement laws and regulations and subjects us to contractual remedies as well as administrative, civil, and criminal sanctions. In addition, the VHCA requires manufacturers participating in Medicaid to agree to provide different mandatory discounts to certain Public Health Service grantees and other safety net hospitals and clinics under the 340B Drug Pricing Program and report the ceiling price to HRSA within HHS. Manufacturers can be audited by HRSA and be subjected to civil monetary penalties for knowingly and intentionally overcharging covered entities for drugs.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, also created federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, a healthcare benefit program, regardless of whether the payor is public or private, knowingly and willfully embezzling or stealing from a health care benefit program, willfully obstructing a criminal investigation of a health care offense, and knowingly and willfully falsifying, concealing, or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items, or services relating to healthcare matters. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it.

Further, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and its respective implementing regulations, extended certain requirements relating to the privacy, security, and transmission of individually identifiable health information directly to business associates and HIPAA-covered entities. While we would not be a "covered entity" under HIPAA, it is possible that we may enter into a service or business arrangement that would cause us to serve as a business associate, defined as a person or organization, other than a member of a covered entity's workforce, that performs certain functions or activities that involve the use or disclosure of protected health information on behalf of, or provides services to, a covered entity. We are not a covered entity under HIPAA but in certain limited situations, we may be considered a business associate. HITECH also strengthened the civil and criminal penalties that may be imposed against covered entities, business associates, and individuals, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, other federal and state laws may govern the privacy and security of health and other information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Even for entities that are not deemed "covered entities" or "business associates" under HIPAA, according to the United States Federal Trade Commission, or the FTC, failing to take appropriate steps to keep consumers' personal information secure constitutes unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act, or the FTCA, 15 USC § 45(a). The FTC expects a company's data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business, and the cost of available tools to improve security and reduce vulnerabilities. Medical data is considered sensitive data that merits stronger safeguards. The FTC's guidance for appropriately securing consumers' personal information is similar to what is required by the HIPAA Security Rule. The FTC's authority under Section 5 is concurrent with HIPAA's jurisdiction and with any action taken under state law.

In addition to the laws discussed above, we may see more stringent state and federal privacy legislation in the future, as the increased cyber-attacks during the pandemic have heightened attention to data privacy and security in the U.S. and other jurisdictions. We cannot predict where new legislation might arise, the scope of such legislation, or the potential impact to our business and operations.

In addition, other federal and state laws may govern the privacy and security of health and other information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. For example, California recently enacted legislation – the California Consumer Privacy Act, or CCPA, which became effective January 1, 2020. The CCPA was recently amended and expanded by the California Privacy Rights Act, or CPRA, which passed on November 3, 2020 and became effective on January 1, 2023. The CPRA's expansion of the "Right to Know" impacts personal information collected on or after January 1, 2022. Companies must still comply with the CCPA during the ramp up period before the CPRA goes into effect. The CCPA and CPRA, among other things, create new data privacy obligations for covered companies and provided new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also created a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach. It remains unclear what, if any, additional modifications will be made to the CPRA by the California legislature or how it will be interpreted. Therefore, the effects of the CCPA and CPRA are significant and will likely require us to modify our data processing practices and may cause us to incur substantial costs and expenses to comply.

Many states have also adopted laws similar to each of the above federal laws, which may be broader in scope and apply to items or services reimbursed by any third-party payor, including commercial insurers, and some have transparency laws that require reporting price increases and related information. Certain state laws also regulate manufacturers' use of prescriber identifiable data. Certain states also require implementation of commercial compliance programs and compliance with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government, or otherwise restrict payments or the provision of other items of value that may be made to healthcare providers and other potential referral sources; impose restrictions on marketing practices; or require drug manufacturers to track and report information related to payments, gifts, and other items of value to physicians and other healthcare providers. These laws may affect our future sales, marketing, and other promotional activities by imposing administrative and compliance burdens.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under such laws, it is possible that certain business activities could be subject to challenge under one or more of such laws. The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions among pharmaceutical companies, providers and patients, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring that business arrangements with third parties comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time- and resource-consuming and can divert management's attention from the business, even if investigators ultimately find that no violation has occurred.

If our operations are found to be in violation of any of the laws or regulations described above or any other laws that apply to us, we may be subject to penalties or other enforcement actions, including criminal and significant civil monetary penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government healthcare programs, corporate integrity agreements, debarment from receiving government contracts or refusal of new orders under existing contracts, reputational harm, diminished profits and future earnings, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post marketing requirements, including safety surveillance, anti fraud and abuse laws, implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

Coverage and Reimbursement Generally

The commercial success of our products depends in part on the extent to which governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers, and other third-party payors provide coverage for and establish adequate reimbursement levels for our product candidates. Government authorities, private health insurers, and other organizations generally decide which drugs they will pay for and establish reimbursement levels and potential access restrictions. Medicare is a federally funded program managed by CMS through local contractors that administer coverage and reimbursement for certain healthcare items and services furnished to the elderly and disabled. Medicaid is an insurance program for certain categories of patients whose income and assets fall below state-defined levels and who are otherwise uninsured that is both federally and state funded and managed by each state. The federal government sets general guidelines for Medicaid and each state creates specific regulations that govern its individual program, including supplemental rebate programs that prioritize coverage for drugs on the state Preferred Drug List. Similarly, government laws and regulations establish the parameters for coverage of prescription drugs by Tricare, the health care program for military personnel, retirees, and related beneficiaries. Many states have also created pharmacy assistance programs for individuals who do not qualify for federal programs. In the United States, private health insurers and other third-party payors often provide reimbursement for products and services based on the level at which the government provides reimbursement through the Medicare or Medicaid programs for such products and services.

In the United States, the European Union, and other potentially significant markets for our product candidates, government authorities and third-party payors are increasingly attempting to limit or regulate the price of medical products and services, particularly for new and innovative products and therapies, which often has resulted in average selling prices lower than they would otherwise be. For example, in the United States, federal and state governments reimburse covered prescription drugs at varying rates generally below average wholesale price. Governmental and private payors may also establish certain access restrictions, such as prior approvals or evidence of failure on existing medications or therapies. These restrictions and limitations influence the purchase of healthcare services and products. Third-party payors are developing increasingly sophisticated methods of controlling healthcare costs. Third-party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drug products for a particular indication. Third-party payors also control costs by requiring prior authorization or imposing other dispensing restrictions before covering certain products and by broadening therapeutic classes to increase competition. Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. Absent clinical differentiators, third-party payors may treat products as therapeutically equivalent and base formulary decisions on net cost. To lower the prescription cost, manufacturers frequently rebate a portion of the prescription price to the third-party payors.

Federal programs also impose price controls through mandatory ceiling prices on purchases by federal agencies and federally funded hospitals and clinics and mandatory rebates on retail pharmacy prescriptions paid by Medicaid and Tricare. These restrictions and limitations influence the purchase of healthcare services and products. Legislative proposals to reform healthcare or reduce costs under government programs may result in lower reimbursement for our product candidates or exclusion of our product candidates from coverage. In addition, government programs like Medicaid include substantial penalties for increasing commercial prices over the rate of inflation which can affect realization and return on investment.

Private payors often rely on the lead of the governmental payors in rendering coverage and reimbursement determinations. Therefore, achieving favorable CMS coverage and reimbursement is usually a significant gating issue for successful introduction of a new product. In addition, many government programs, as a condition of participation, mandate fixed discounts or rebates from manufacturers regardless of formulary position or utilization, and then rely on competition in the market to attain further price reductions, which can greatly reduce realization on the sale.

Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the European Union will put additional pressure on product pricing, reimbursement, and utilization, which may adversely affect our future product sales and results of operations. These pressures can arise from rules and practices of managed care groups and health technology assessment bodies, competition within therapeutic classes, availability of generic equivalents, judicial decisions and governmental laws and regulations related to Medicare, Medicaid, and healthcare reform, pharmaceutical coverage and reimbursement policies, and pricing in general. Patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Sales of our products will therefore depend substantially, both domestically and abroad, on the extent to which the costs of our products will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, such as Medicare and Medicaid, private health insurers, and other third-party payors.

As a result of the above, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain the FDA and other comparable foreign regulatory authority approvals. Our products may not be considered medically necessary or cost-effective, or the rebate percentages required to secure coverage may not yield an adequate margin over cost.

There is often pressure to renegotiate pricing and reimbursement levels, including, in particular, in connection with changes to Medicare. Third-party payors continue to demand discounted fee structures, and the trend toward consolidation among third-party payors tends to increase their bargaining power over price structures. If third-party payors reduce their rates for our products, then our revenue and profitability may decline, and our operating margins will be reduced. Because some third-party payors rely on all or portions of Medicare payment systems to determine payment rates, changes to government healthcare programs that reduce payments under these programs may negatively impact payments from third-party payors. Our inability to maintain suitable financial arrangements with third-party payors could have a material adverse impact on our business. Additionally, the reimbursement process is complex and can involve lengthy delays. Third-party payors may disallow, in whole or in part, providers' requests for reimbursement based on determinations that certain amounts are not reimbursable under plan coverage, that the drugs provided were not medically necessary, or that additional supporting documentation is necessary. Retroactive adjustments may change amounts realized from third-party payors. Delays and uncertainties in the reimbursement process may adversely affect market acceptance and utilization of our products, resulting in reduced revenues. The unavailability or inadequacy of third-party coverage and reimbursement could negatively affect the market acceptance of our products and the future revenues we may expect to receive from those products. In addition, we are unable to predict what additional legislation or regulation relating to the healthcare industry or third-party coverage and reimbursement may be enacted in the future, or what effect such legislation or regulation would have on our business. Many hospitals implement a controlled and defined process for developing and approving formularies. Any marketing efforts that are determined to have violated such policies could result in the denial or removal of our products from that hospital's formulary.

Moreover, a payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our products or exclusion of our products from coverage. The cost containment measures that healthcare payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates. We cannot provide any assurances that we will be able to obtain and maintain third-party coverage or adequate reimbursement for our product candidates in whole or in part.

Pharmacy benefit managers, or PBMs, rebates and pricing transparency are key areas of legislative and regulatory focus and there may be changes in the regulatory landscape that could have a significant impact on the pharmaceutical supply chain and drug pricing more generally, which could affect our business operations and prospects in unknown and material ways.

Healthcare Reform Measures

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals designed to change the healthcare system in ways that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities, and affect our ability to sell our products profitably. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality, and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

For example, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act, or, collectively, the ACA has substantially changed and continues to impact healthcare financing and delivery by both government payors and private insurers. Among the ACA provisions of importance to the pharmaceutical industry, in addition to those otherwise described above, are the following:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain federal programs identified in the ACA;

- expansion of beneficiary eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 138% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expansion of manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price" for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- a separate methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected;
- expansion of the types of entities eligible for the 340B drug discount program;
- establishment of the Medicare Part D coverage gap discount program that, as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D, requires manufacturers to provide a now 70% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period;
- establishment of the Center for Medicare and Medicaid Innovation within the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending;
- creation of the Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- reporting of certain financial arrangements between manufacturers of drugs, biologics, devices, and medical supplies and physicians and teaching hospitals under the Sunshine Act; and
- annual reporting of certain information regarding drug samples that manufacturers and distributors provide to licensed practitioners.

The ACA established the Patient-Centered Outcome Research Institute to organize and coordinate federally funded research to compare the effectiveness of different treatments for the same illness. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of any product, if any such product or the condition that it is intended to treat is the subject of a study. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates. If third-party payors do not consider our product candidates to be cost-effective compared to other available therapies, they may not cover our product candidates, once approved, as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The ACA made other changes intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for healthcare and health insurance industries, impose new taxes and fees on the health care industry, and impose additional health policy reforms. The law expanded the eligibility criteria for Medicaid programs, thereby potentially increasing both the volume of sales and manufacturers' Medicaid rebate liability. The law also expanded the entities eligible for discounts under the 340B Drug Discount Program, which mandates discounts to certain hospitals, community centers, and other qualifying providers, although, with the exception of children's hospitals, these newly eligible entities are not eligible to receive discounted 340B pricing on orphan drugs and the Health Resources and Services Administration has narrowed its interpretation of which beneficiaries may fill prescriptions through 340B inventories. The law additionally extended manufacturer's Medicaid rebate liability to covered drugs dispensed to patients enrolled in Medicaid managed care organizations, increased the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate program, and created an alternative rebate formula for certain new formulations of certain existing products, which is intended to increase the amount of rebates due on those drugs. The revisions to the Medicaid rebate formula can have the further effect of increasing the required 340B discounts. Finally, the ACA imposes a significant annual fee on companies that manufacture or import branded prescription drug products. Substantial new provisions affecting compliance have also been enacted through the ACA and otherwise, including the reporting of drug sample distribution, which may require us to modify our business practices with healthcare practitioners. Moreover, in the coming years, additional changes could be made to governmental healthcare programs that could significantly impact the success of our products.

The ACA also imposed an affirmative obligation to report and repay any overpayments, including those payments that resulted from violations of the Anti-Kickback Statute, FCA, or Civil Monetary Penalties Law, within sixty (60) days after such overpayment has been identified. Corresponding case law imposes an obligation on entities to exercise reasonable diligence in identifying such overpayments. The failure to timely report and repay is, itself, considered to constitute a violation of the FCA.

The framework of the ACA continues to evolve as a result of executive, legislative, regulatory, and administrative developments that have challenged the law and contribute to legal uncertainty that could affect the profitability of our products. While Congress has not enacted legislation to comprehensively repeal the ACA, legislation affecting the ACA has been signed into law, including the elimination, effective January 1, 2019, of the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly referred to as the "individual mandate."

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established a prescription drug benefit program for Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Part D plans include both standalone prescription drug benefit plans and prescription drug coverage as a supplement to Medicare Advantage plans. Unlike Medicare Part A and B, which do not utilize formularies to restrict coverage, Part D coverage varies by plan. With some exceptions, Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, Part D plans use competition for coverage to leverage manufacturer rebates. Further, the law requires manufacturers to absorb a significant percentage of the prescription price paid for NDA drugs, including 504(b)(2) drugs, during a beneficiary's coverage gap. The Bipartisan Budget Act of 2018 permanently increased manufacturer liability for the prescription price in the coverage gap from 50% to 70% beginning in 2019, while simultaneously accelerating closure of the gap. These cost reduction initiatives and other provisions of the legislation, as well as any negotiated price discounts for our future products covered by a Part D prescription drug plan, may decrease the coverage and reimbursement rate that we receive, lower the net price realized on our sales to pharmacies, or both. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from Medicare Part D may result in a similar reduction in payments from non-governmental payors.

There have been numerous initiatives on the federal and state levels in the United States for comprehensive reforms affecting the payment for, the availability of, and reimbursement for, healthcare services. Current and future U.S. legislative healthcare reforms may result in price controls and other restrictions for any approved products, if covered, and could seriously harm our business. In August 2022, the Inflation Reduction Act of 2022, or the IRA, was signed into law. The IRA includes several provisions that impose new manufacturer financial liability on all drugs in Medicare Part D beginning in 2025, allow the U.S. government to negotiate prices for some drugs covered under Medicare Part D beginning in 2026 and Medicare Part B beginning in 2028, and require companies to pay rebates to Medicare beginning in 2023 for drug prices that increase faster than inflation. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. For that and other reasons, it is currently unclear how the IRA will be effectuated, and the impact of the IRA on the pharmaceutical industry cannot yet be fully determined. On December 14, 2023, President Biden announced that, through the IRA, dozens of pharmaceutical companies are required to pay rebates to Medicare for price hikes on prescription drugs.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. For example, the Budget Control Act of 2011, among other things, resulted in reductions in payments to Medicare providers of 2% per fiscal year, which went into effect on April 1, 2013 and, due to subsequent legislation, will remain in effect through 2031, with the exception of a temporary suspension of the payment reduction from May 1, 2020 through March 31, 2022 due to the coronavirus pandemic. Sequestration began again on April 1, 2022. From April 1, 2022 to June 30, 2022, payments for Medicare fee-for-service claims were adjusted downwards by 1%; beginning on July 1, 2022, the payments were adjusted downwards by 2%. In addition, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminated the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. These legislative changes may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our products or the frequency with which any such product is prescribed or used.

Recently, the cost of prescription pharmaceuticals has been the subject of considerable discussion in the United States. Congress considered and passed legislation, and the former Trump administration pursued several regulatory reforms to further increase transparency around prices and price increases, lower out-of-pocket costs for consumers, and decrease spending on prescription drugs by government programs. Congress also continued to conduct inquiries into the prescription drug industry's pricing practices. While several proposed reform measures will require Congress to pass legislation to become effective, Congress and the Biden administration have each indicated that it will continue to seek new legislative and/or administrative measures to address prescription drug costs. The Biden administration has taken several recent executive actions that signal changes in policy from the prior administration. For example, on July 9, 2021, President Biden signed an executive order to promote competition in the U.S. economy that included several initiatives addressing prescription drugs. Among other provisions, the executive order directed the Secretary of HHS to issue a report to the White House within 45 days that included a plan to, among other things, reduce prices for prescription drugs, including prices paid by the federal government for such drugs. In response to the executive order, on September 9, 2021, HHS issued a Comprehensive Plan for Addressing High Drug Prices that identified potential legislative policies and administrative tools that Congress and HHS can pursue in order to make drug prices more affordable and equitable, improve and promote competition throughout the prescription drug industry, and foster scientific innovation. Additionally, on February 2, 2022, the Biden administration signaled its continued commitment to the Cancer Moonshot initiative, which was initially launched in 2016. In its announcement, the administration noted that its new goals under the initiative include addressing inequities in order to ensure broader access to cutting-edge cancer therapeutics and investing in a robust pipeline for new treatments.

At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological 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. Some states, such as California, have enacted transparency laws that require manufacturers to report drug price increases and related information. The boom in state laws targeting drug pricing is unprecedented and the requirements are not uniform from state to state, creating additional compliance and commercialization challenges for manufacturers. We further expect that the pharmaceutical industry will experience pricing pressures due to the trend toward managed healthcare, the increasing influence of managed care organizations, judicial interpretation of health care reform efforts, and additional legislative and regulatory proposals resulting in ongoing, relatively rapid changes to applicable laws and regulations. Our results of operations could be adversely affected by current and future healthcare reforms.

Government and private payors also increasingly require pre-approval of coverage for new or innovative devices or drug therapies or condition coverage on unsuccessful alternative treatment before they will reimburse healthcare providers that use such therapies. For some specialty drugs, payors are conditioning payment on successful treatment measured by objective metrics. While we cannot predict whether any proposed cost-containment measures will be adopted or otherwise implemented in the future, the announcement or adoption of these proposals could have a material adverse effect on our ability to obtain adequate prices for our products and operate profitably.

In the future, there may continue to be additional proposals relating to the reform of the U.S. healthcare system, some of which could further limit the prices we will be able to charge for our products, or the amounts of reimbursement available for our products. We continue to monitor the potential impact of proposals to lower prescription drug costs at the federal and state level. Managed care organizations, as well as Medicaid and other government agencies, continue to seek price discounts. Some states have implemented, and other states are considering, measures to reduce costs of the Medicaid program, and some states are considering implementing measures that would apply to broader segments of their populations that are not Medicaid-eligible. Due to the volatility in the current economic and market dynamics, we are unable to predict the impact of any unforeseen or unknown legislative, regulatory, payor or policy actions, which may include cost containment and healthcare reform measures. Such policy actions could have a material adverse impact on our profitability.

These and other healthcare reform initiatives may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on our financial operations. We expect that additional state and federal 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 reduced demand for our products or additional pricing pressures.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act of 1977, or FCPA, prohibits any U.S. individual or business from paying, offering, or authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party, or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations. Activities that violate the FCPA, even if they occur wholly outside the United States, can result in criminal and civil fines, imprisonment, disgorgement, oversight, and debarment from government contracts.

Foreign Regulation

We are subject to a variety of foreign regulatory requirements regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales, and distribution of our products. For example, in the European Union, or EU, Regulation (EU) 536/2014 on clinical trials, or CTR, requires sponsors to submit a single clinical trial application, or CTA, through the Clinical Trials Information System, or CTIS, an online portal to streamline the authorization process. While under the previously applicable Directive 2001/20/EC, or CTD, sponsors had to request separate approvals in each EU/EEA member state, the CTIS is a single-entry point that allows sponsors to apply for authorization to run a clinical trial in up to 30 EU/EEA countries. The CTIS authorization procedure is composed of two parts: (i) member states jointly cooperate during the Part I assessment of the applicable CTA and (ii) during Part II, the applicable CTA is assessed by each member state individually. All ongoing clinical trials in the EU/EEA were required to transition to the CTIS by January 30, 2025. This date marked the end of a three-year transition period that began when the CTR became applicable. Whether or not we obtain FDA approval for a product, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing, and reimbursement vary greatly from country to country. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others. As in the United States, post approval regulatory requirements, such as those regarding product manufacture, marketing, or distribution, would apply to any product that is approved outside the United States.

European Union Drug Approval Process

To obtain a marketing authorization of a drug in the European Union, we may submit marketing authorization applications, or MAAs, either under the so-called centralized, decentralized, mutual recognition, or national authorization procedures.

Centralized Procedure

In the centralized procedure, the European Commission, or EC, grants a single marketing authorization following a favorable opinion by the European Medicines Agency, or EMA, which is valid in all European Union member states, as well as in the European Economic Area, or EEA, countries (Iceland, Liechtenstein, and Norway). The centralized procedure is compulsory for medicines produced by specified biotechnological processes, products designated as orphan medicinal products, advanced-therapy medicinal products, or ATMPs, and products with a new active substance indicated for the treatment of specified diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders, autoimmune diseases and other immune dysfunctions, or viral diseases. The centralized procedure is optional for products containing new active substances for indications other than those stated above, products that represent a significant therapeutic, scientific, or technical innovation, or whose authorization would be in the interest of public health. Under the centralized procedure, the maximum timeframe for the evaluation of an MAA by the EMA is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee for Medicinal Products for Human Use, or the CHMP. Accelerated assessment might be granted by the CHMP in exceptional cases, such as when a medicinal product is expected to be of a major public health interest, particularly from the point of view of therapeutic innovation. The timeframe for the evaluation of an MAA under the accelerated assessment procedure is 150 days, excluding clock stops.

Authorization Procedures

There are also other possible routes to authorize medicinal products in several European Union countries, which are available for investigational medicinal products that fall outside the scope of the centralized procedure:

- *Decentralized procedure.* Using the decentralized procedure, an applicant may apply in more than one European Union country in parallel, although the applicant must nominate one reference European Union Member State, for simultaneous authorization of medicinal products that have not yet been authorized in any European Union country and that do not fall within the mandatory scope of the centralized procedure. Failing agreement, there is a procedure for resolving disagreements between member states and ultimately an arbitration procedure before the CHMP.

- *Mutual recognition procedure.* In the mutual recognition procedure, a medicine is first authorized in one European Union Member State, referred to as the reference member state, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other nominated European Union countries, referred to as the concerned member states, in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization. The procedure for disagreements described above similarly applies.

- *National procedures.* Purely national procedures continue to be possible but are strictly limited to where the product is to be authorized in one member state only.

In the European Union, new products authorized for marketing, referred to as reference products, qualify for eight years of data exclusivity and an additional two years of market exclusivity upon marketing authorization. The data exclusivity period prevents generic applicants from relying on the preclinical and clinical trial data contained in the dossier of the reference product when applying for a generic marketing authorization in the European Union during a period of eight years from the date on which the reference product was first authorized in the European Union. The market exclusivity period prevents a successful generic applicant from commercializing its product in the European Union until 10 years have elapsed from the initial authorization of the reference product in the European Union. The 10-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Overall, this period of regulatory data protection, or RDP, is commonly referred to as the "8+2+1" approach. This period of RDP equally applies to medicinal products that are authorized through the national procedure (or decentralized or mutual recognition procedures) under national law or through the centralized procedure.

Research and Development

Conducting research and development is central to our business model. We have invested and expect to continue to invest significant time and capital in our research and development operations. Our research and development expenses were $187.1 million, and $97.9 million for the years ended December 31, 2024 and 2023, respectively. Research and development expenses are expected to stabilize in the near term as certain development programs near completion while new development programs are initiated.

Employees and Human Capital Management

As of February 11, 2025, we had 683 full-time employees. None of our employees are represented by a collective bargaining agreement and we have never experienced any work stoppage. We believe that we maintain good relations with our employees. Our employees are highly skilled, and many hold advanced degrees. Many of our employees have experience with drug commercialization or development. Our future performance depends significantly upon the continued service of our key scientific, technical and senior management personnel and our continued ability to attract and retain highly skilled employees. We provide our employees with competitive salaries and bonuses, opportunities for equity ownership, development programs that enable continued learning and growth and a robust employment package that promotes well-being across all aspects of their lives. In addition to salaries, these programs include potential annual discretionary bonuses, stock awards, healthcare and insurance benefits, health savings and flexible spending accounts, paid time off, family leave, and flexible work schedules, among other benefits. We may take further actions, in compliance with all appropriate government regulations, that we determine to be in the best interest of our employees.

Corporate Information

We were incorporated in Delaware in January 2012. Our offices are located at One World Trade Center 22nd Floor, New York, New York 10007, and our telephone number is (212) 332-3241.

Available Information

We file reports and other information with the SEC, as required by the Exchange Act. We make available free of charge through our website (http://www.axsome.com) our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "Investors," as a source of information about us. The foregoing references to our website are not intended to, nor shall they be deemed to, incorporate information on our website into this Annual Report on Form 10-K by reference.

ITEM 1A. RISK FACTORS.

The Company is subject to a number of risks that if realized could materially adversely affect its business, results of operations, cash flow, financial condition or prospects. The following is a summary of the principal risk factors facing the Company. The list below is not exhaustive, and the Company faces additional challenges and risks. Investors should carefully consider all of the information set forth in this Annual Report on Form 10-K, including the following risk factors, before deciding to invest in any of the Company's securities.

Risk Factors Summary

Our business is subject to a number of risks and uncertainties, including those risks discussed at length below. These risks include, among others, the following:

- ***We have incurred significant losses since our inception, anticipate that we will continue to have losses, and may never achieve or maintain profitability.***

- ***We may need additional funding to conduct our future clinical trials and to complete development and commercialization of our product candidates. If we are unable to raise capital when needed, we would be forced to delay, reduce, or eliminate our product development programs or commercialization efforts.***

- ***Our operating activities may be restricted as a result of covenants related to the outstanding indebtedness under our loan and security agreement with Hercules and we may be required to repay the outstanding indebtedness in an event of default, which could have a materially adverse effect on our business.***

- ***We have a limited operating history of commercializing products, which may make it difficult to evaluate our business and prospects.***

- ***We are substantially dependent on the success of our products and cannot guarantee that any of our product candidates will successfully complete any planned or ongoing clinical trials, receive regulatory approval, or be successfully commercialized.***

- ***If safety and efficacy data for our product candidates, a reference drug, or published literature does not satisfactorily demonstrate safety and efficacy to the FDA, or if the FDA and other regulators do not permit us to rely on the data of a reference drug or published literature, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.***

- ***Although Breakthrough Therapy, Fast Track, and other designations are designed to expedite the development and review of drugs, they may not ultimately lead to a faster approval process or faster development of regulatory review, and they will not increase the likelihood that our product candidates will receive marketing approval, for example, Breakthrough Therapy designation by the FDA for AXS-05 for the treatment of AD agitation.***

- ***We face significant competition from other pharmaceutical and biotechnology companies, academic institutions, government agencies, and other research organizations. Our operating results will suffer if we fail to compete effectively.***

- ***If we are unable to establish effective marketing, sales and distribution capabilities or enter into agreements with third parties to market, sell and distribute our products, we may be unable to generate substantial product revenues.***

- ***If any of our products do not achieve broad market acceptance, we may be unable to generate substantial product revenues.***

- ***We rely, and expect to continue to rely, on third parties to perform many essential services for our products and product candidates, including services related to our preclinical studies and clinical trials, warehousing and inventory control, distribution, government price reporting, customer service, and adverse event reporting. If these third parties fail to perform satisfactorily, including by failing to meet deadlines for the completion of our preclinical studies and clinical trials, or fail to comply with legal and regulatory requirements, our ability to commercialize any of our products will be significantly impacted and we may be subject to regulatory sanctions.***

- ***If the manufacturers upon whom we rely fail to produce our products in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose or fail to generate potential revenues.***

- ***Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.***

- ***We have licensed and may need to license certain intellectual property from third parties in the future. Such licenses may not be available or may not be available on commercially reasonable terms. Our business may be materially harmed if the licenses are not available or terminated for any reason.***

- ***If we fail to comply with federal, state, and foreign healthcare laws, including laws governing fraud and abuse, transparency, health and other data protection, information privacy and security, we could face substantial penalties and liabilities, and our business, financial condition, results of operations, and prospects could be adversely affected.***

- ***If the government or third-party payors fail to provide adequate coverage and payment rates for any of our products, or if such payors and health care providers including health maintenance organizations (HMOs) and long-term care facilities choose to use therapies that are less expensive, our revenue and prospects for profitability may be limited.***

- ***We have and may continue to significantly increase the size of our organization, and we may experience difficulties in managing growth. If we are unable to implement appropriate controls and procedures to manage our growth, we will not be able to implement our business plan successfully.***

- ***If we fail to maintain an effective system of internal controls over financial reporting, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common stock.***

- ***Our principal stockholders and management own a significant percentage of our stock and may be able to exert significant control over matters subject to stockholder approval.***

- ***The use of our net operating loss carryforwards and research tax credits may be limited.***

RISKS RELATED TO OUR FINANCIAL CONDITION AND CAPITAL REQUIREMENTS

We have incurred significant losses since our inception, anticipate that we will continue to have losses, and may never achieve or maintain profitability.

We are a biopharmaceutical company with a limited operating history. Since inception, we have incurred significant operating losses. Our net loss was $287.2 million for the year ended December 31, 2024. As of December 31, 2024, we had an accumulated deficit of $1,122.8 million. In 2022, we commenced the commercial sale of Auvelity in the United States and Sunosi in the United States and select global markets. In January 2025, Symbravo® was approved by the FDA for the acute treatment of migraine with or without aura in adults. Apart from Auvelity, Sunosi, and Symbravo, we have no other products which have received regulatory approval.

We expect to continue to incur substantial expenses and operating losses, as we continue to develop our current and future product candidates. In addition, we expect to incur significant sales, marketing, and manufacturing expenses related to the commercialization of Auvelity, Sunosi, Symbravo, and any other product candidate which the FDA may approve or which we may in-license. We anticipate that our expenses will increase substantially as we:

- seek regulatory approval for additional product candidates;
- hire additional commercial, clinical, medical, quality, regulatory, and scientific personnel;
- add operational, financial, and management information systems and personnel;
- expand our sales, marketing, and distribution infrastructure;
- expand external manufacturing capabilities and production to commercialize any additional products for which we may obtain regulatory approval and that we choose not to license to a third party;
- undertake additional manufacturing activities of our product candidates to satisfy FDA requirements for marketing application submissions;
- continue to evaluate, plan for, and conduct clinical trials for AXS-05 as an aid to smoking cessation treatment and other CNS disorders;
- continue to evaluate, plan for, and conduct clinical trials for solriamfetol in additional indications;
- continue to evaluate, plan for, and potentially submit NDAs for other pipeline products;
- continue to expand commercial sales of Auvelity and Sunosi;
- commercially launch Symbravo;
- develop, in-license, or acquire additional product candidates;
- conduct late-stage clinical trials for any product candidates that successfully complete early-stage clinical trials;
- conduct additional non-clinical studies with any product candidates; and
- maintain, expand, and protect our intellectual property portfolio.

To become and remain profitable, we must succeed in developing (or in-licensing) and commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, which may include completing preclinical testing and clinical trials of our product candidates, discovering additional product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing, and selling any products for which we may obtain regulatory approval, achieving market acceptance of our products, satisfying any post-marketing requirements, maintaining appropriate distribution, setting prices, and obtaining reimbursement for our products from private insurance or government payors. We are only in the preliminary stages of some of these activities with respect to certain products and product candidates. We may never succeed in some of these activities and, even if we do, may never achieve profitability.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses we may incur or when, or if, we will be able to achieve profitability. If we are required by the FDA or comparable foreign regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

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 the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings, continue the commercialization of our products, or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We may need additional funding to conduct our future clinical trials and to complete development and commercialization of our product candidates. If we are unable to raise capital when needed, we would be forced to delay, reduce, or eliminate our product development programs or commercialization efforts.

Conducting clinical trials, pursuing regulatory approvals, establishing outsourced manufacturing relationships, and successfully manufacturing and commercializing our product candidates is a time-consuming, expensive, and uncertain process that takes years to complete. We may need to raise additional capital to:

- fund our future clinical trials for our current product candidates, especially if we encounter any unforeseen delays or difficulties in our planned development activities;
- fund our operations and continue to commercialize our products;
- qualify and outsource the commercial scale manufacturing of our products under cGMP;
- develop additional product candidates; and
- in-license other product candidates.

We believe that our current cash is sufficient to fund anticipated operations into cash flow positivity, based on the current operating plan. Our assumptions may prove to be wrong, and we could spend our available financial resources faster than we currently expect. Further, we may not have sufficient financial resources to meet all of our objectives. Our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress and costs related to the development of our product candidates, including the costs of preparing filings for regulatory approval;
- the costs associated with conducting additional clinical and non-clinical studies with any of our product candidates;
- the potential for delays in our efforts to seek regulatory approval for our product candidates, and any costs associated with such delays;

- the costs associated with selling, marketing, and distributing our approved products;
- the costs of filing, prosecuting, defending, and enforcing any patent claims and other intellectual property rights associated with our product candidates;
- the cost and timing of manufacturing, or having third parties manufacture, sufficient supplies of our product candidates in preparation for commercialization;
- the effect of competing technological and market developments;
- revenues from commercial sales of our approved products;
- the terms and timing of any collaborative, licensing, co-promotion, or other arrangements that we may establish; and
- the success of the commercialization of any of our current products and, if approved, any of our product candidates.

Future capital requirements will also depend on the extent to which we acquire or invest in additional businesses, products, and technologies. Until we can generate a sufficient amount of product revenue, if ever, we may finance future cash needs through public or private equity offerings, debt financings, royalties, and corporate collaboration and licensing arrangements, as well as through interest income earned on cash and investment balances. We cannot be certain that additional funding will be available on acceptable terms, or at all. If adequate funds are not available, we may be required to delay, reduce the scope of, or eliminate one or more of our development programs or our commercialization efforts.

Our operating activities may be restricted as a result of covenants related to the outstanding indebtedness under our loan and security agreement with Hercules and we may be required to repay the outstanding indebtedness in an event of default, which could have a materially adverse effect on our business.

In September 2020, we entered into a Loan and Security Agreement, or the Loan Agreement, for a term loan, which we refer to as the 2020 Term Loan, with Hercules Capital, Inc., or Hercules, in its capacity as administrative agent and collateral agent and as a lender, and the other financial institutions that from time to time become parties to the Loan Agreement, collectively referred to as the Lenders, secured by a lien on substantially all of our assets, including intellectual property. In October 2021, we entered into a First Amendment to the Loan Agreement to, among other things, increase the size of the 2020 Term Loan. In March 2022, we entered into a Second Amendment to the Loan Agreement that, among other things, changed the terms of the Term Loan Advances (as defined in the Loan Agreement) upon the consummation of the Acquisition (as defined in the Loan Agreement). In January 2023, we entered into the Third Amendment, which amended the terms of the Loan Agreement to, among other things, increase the size of the aggregate principal amount under the 2020 Term Loan from $300.0 million to $350.0 million, reduce the interest rate, and extend the maturity and interest-only period of the Loan Agreement. In May 2023, we entered into the Fourth Amendment, which increased the amount of cash that could be held by the Malta Subsidiary outside of the United States and waived any purported default with respect to the amount of cash held by the Malta Subsidiary prior to the date of the Fourth Amendment. In August 2023, Hercules granted Axsome a waiver to the Fourth Amendment, increasing the amount of cash that could be held by the Malta Subsidiary outside of the United States until December 31, 2023. In September 30, 2024, we entered into the Fifth Amendment, which amended the terms of the Loan Agreement to, among other things: (i) increase the size of the aggregate principal amount under tranche 3 of the 2020 Term Loan from $75.0 to $80.0 million; (ii) extend the availability periods of certain tranches of the 2020 Term Loan; (iii) alter the terms of the performance covenants contained in the Loan Agreement and also add a new performance covenant; (iv) conditionally waive the minimum cash requirement during such periods of time that Axsome's market capitalization exceeds $1.5 billion; and (v) permit the Malta Subsidiary to request an advance from the Lenders up to a certain amount to the extent that Axsome may request an advance in such amount and to increase the amount of cash that the Malta Subsidiary may hold outside of the United States, as set forth in greater detail in the Fifth Amendment.

The Loan Agreement contains various covenants that limit our ability to engage in specified types of transactions. These covenants limit our ability to, among other things, sell, transfer, lease or dispose of certain assets; incur indebtedness; encumber or permit liens on certain assets; make certain investments; make certain restricted payments, including paying dividends on, or repurchasing or making distributions with respect to, our common stock; and enter into certain transactions with affiliates. Our business may be adversely affected by these restrictions on our ability to operate our business.

The covenants under the Loan Agreement also require maintaining a minimum amount of cash in an account or accounts in which the Lenders have a first priority security interest.

A breach of any of the covenants under the Loan Agreement could result in a default under the 2020 Term Loan. Upon the occurrence of an event of default under the 2020 Term Loan, the Lenders could elect to declare all amounts outstanding, if any, to be immediately due and payable and terminate all commitments to extend further credit. If there are any amounts outstanding that we are unable to repay, the Lenders could proceed against the collateral granted to it to secure such indebtedness.

We have a limited operating history of commercializing products, which may make it difficult to evaluate our business and prospects.

We are a commercial-stage company. Prior to our commercialization of Auvelity and Sunosi in 2022, and the recent approval of Symbravo, we had not obtained marketing approvals for any product candidates, manufactured products on a commercial scale or arranged for a third party to do so on our behalf, or conducted sales and marketing activities necessary for successful commercialization. Consequently, predictions about our future success or viability may not be as accurate as they would be if we had a longer history of successfully developing and commercializing products.

We expect our financial condition and operating results to continue to fluctuate from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. We have transitioned from a company with solely a research and development focus to a company also capable of undertaking commercial activities. We may continue to encounter unforeseen expenses, difficulties, complications and delays, and this may not be a successful transition.

We are currently operating in a period of economic uncertainty and capital markets disruption, which has been significantly impacted by geopolitical instability, ongoing military conflicts between Russia and Ukraine and between Israel and Hamas, Hezbollah, and the Houthis, and record inflation. Our business, financial condition, and results of operations could be materially adversely affected by any negative impact on the global economy and capital markets resulting from the conflicts in Ukraine and the Middle East, geopolitical tensions, or record inflation.

U.S. and global markets are experiencing volatility and disruption following the escalation of geopolitical tensions and the start of the military conflict between Russia and Ukraine. On February 24, 2022, a full-scale military invasion of Ukraine by Russian troops was reported. Although the length and impact of the ongoing military conflict is highly unpredictable, the conflict in Ukraine could lead to market disruptions, including significant volatility in commodity prices, credit and capital markets, as well as supply chain interruptions. We are continuing to monitor the situation in Ukraine and globally and assessing its potential impact on our business.

Additionally, the military conflict in Ukraine has led to sanctions and other penalties being levied by the United States, European Union and other countries against Russia. Additional potential sanctions and penalties have also been proposed and/or threatened. Russian military actions and the resulting sanctions could adversely affect the global economy and financial markets and lead to instability and lack of liquidity in capital markets, potentially making it more difficult for us to obtain additional funds.

In addition, on October 7, 2023, Hamas militants and members of other terrorist organizations infiltrated Israel's southern border from the Gaza Strip and conducted a series of terror attacks on civilian and military targets. Shortly following the attack, Israel's security cabinet declared war against Hamas, and Israel launched an aerial bombardment of various targets within the Gaza Strip and then also began ground operations in the Gaza Strip, which remain ongoing. Other terrorist and/or regional organizations have joined the hostilities as well, including Hezbollah in Lebanon, and the Houthis in Yemen, and it is possible that other countries in the Middle East, including Iran, will become further involved in hostilities with Israel, resulting in a further widening of the conflict. The intensity and duration of Israel's current wars are difficult to predict as are such wars' implications for the global economy.

Although our business has not been materially impacted by these geopolitical issues, or the U.S. domestic political climate, to date, it is impossible to predict the extent to which our operations, or those of our suppliers and manufacturers, will be impacted in the short and long term, or the ways in which conflicts may impact our business. The extent and duration of military action, sanctions, and resulting market disruptions are impossible to predict, but could be substantial. Any such disruptions may also magnify the impact of other risks described herein.

Political uncertainty may have an adverse impact on our operating performance and results of operations.

General political uncertainty may have an adverse impact on our operating performance and results of operations. In particular, the U.S. continues to experience significant political events that cast uncertainty on global financial and economic markets, especially following the recent presidential election. It is presently unclear exactly what actions the second Trump administration in the U.S. will implement, and if implemented, how these actions may impact the biopharmaceutical industry in the U.S. Any actions taken by the Trump administration, including the many recent executive orders, may have a negative impact on the U.S. economy and on our business, financial condition, and results of operations.

Climate change or legal, regulatory or market measures to address climate change may negatively affect our business, results of operations, cash flows and prospects.

We believe that climate change has the potential to negatively affect our business and results of operations, cash flows and prospects. We are exposed to physical risks (such as extreme weather conditions or rising sea levels), risks in transitioning to a low-carbon economy (such as additional legal or regulatory requirements, changes in technology, market risk, and reputational risk) and social and human effects (such as population dislocations and harm to health and well-being) associated with climate change. These risks can be either acute (short-term) or chronic (long-term).

The adverse impacts of climate change include increased frequency and severity of natural disasters and extreme weather events such as hurricanes, tornados, wildfires (exacerbated by drought), flooding, and extreme heat. Extreme weather and sea-level rise pose physical risks to our facilities as well as those of our suppliers. Such risks include losses incurred as a result of physical damage to facilities, loss or spoilage of inventory, and business interruption caused by such natural disasters and extreme weather events. Other potential physical impacts due to climate change include reduced access to high-quality water in certain regions and the loss of biodiversity, which could impact future product development. These risks could disrupt our operations and its supply chain, which may result in increased costs.

New legal or regulatory requirements may be enacted to prevent, mitigate, or adapt to the implications of a changing climate and its effects on the environment. These regulations, which may differ across jurisdictions, could result in us being subject to new or expanded carbon pricing or taxes, increased compliance costs, restrictions on greenhouse gas emissions, investment in new technologies, increased carbon disclosure and transparency, upgrade of facilities to meet new building codes, and the redesign of utility systems, which could increase our operating costs, including the cost of electricity and energy used by us. Our supply chain would likely be subject to these same transitional risks and would likely pass along any increased costs to us.

RISKS RELATED TO OUR BUSINESS AND THE DEVELOPMENT OF OUR PRODUCT CANDIDATES

We are substantially dependent on the success of our products and cannot guarantee that any of our product candidates will successfully complete any planned or ongoing clinical trials, receive regulatory approval, or be successfully commercialized.

We currently have three products approved for commercial distribution. We have invested a significant portion of our efforts and financial resources in the development of our product candidates. Our business, including our ability to generate revenue, depends entirely on the successful commercialization of Auvelity, Sunosi, and Symbravo, and the successful development and commercialization of our product candidates and/or future in-licensing activities, which may never occur. Furthermore, given the nature of our business, the biopharmaceutical industry in general and the uncertainty and costs associated with developing and commercializing our products within a complicated and costly regulatory regime, our goals, plans and assumptions with respect to our products may evolve or change. For example, we may not continue to emphasize, focus our research and development efforts on or direct resources to certain of our product candidates, and we may shift our focus and resources to our other current or future products. Any such change in our business strategy could harm our business, cause uncertainty or confusion in the marketplace or harm the clinical prospects of our products.

Our product candidates will require additional clinical and non-clinical development, regulatory approval, commercial manufacturing arrangements, significant marketing efforts, and further investment before we generate any revenues from the sale of such product candidates. Multiple clinical trials are ongoing. As a result of one or more risks discussed in this section, we cannot assure you that we will meet projected timelines related to these trials.

We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates. Even if our product candidates are approved, they may be subject to limitations on the indicated uses for which they may be marketed, distribution restrictions, or to other conditions of approval, may contain significant safety warnings, including boxed warnings, contraindications, and precautions, may not be approved with label statements necessary or desirable for successful commercialization, or may contain requirements for costly post-market testing and surveillance, or other requirements, including the submission of a REMS to monitor the safety or efficacy of the products. If we do not receive regulatory approval for, and successfully commercialize, our product candidates, we will not be able to generate revenue from these product candidates in the foreseeable future, or at all. Any significant delays in obtaining approval for and commercializing our product candidates will have a material adverse impact on our business and financial condition.

Although we submitted NDAs to the FDA for Auvelity (which was approved) and for Symbravo for the acute treatment of migraines (which received a CRL and has now been approved), we have not otherwise submitted an NDA to the FDA, or similar drug approval filings to comparable foreign authorities, for any product candidate, and we cannot be certain that our current or future product candidates will be successful in clinical trials or receive regulatory approval.

Our product candidates are susceptible to the risks of failure inherent at any stage of product development, including the appearance of unexpected adverse events or failure to achieve its primary endpoints in subsequent clinical trials, including our initiated and planned Phase 3 clinical trials. We conducted one interim analysis for the Phase 2/3 trial of AXS-05 in TRD and one interim analysis for the Phase 2/3 trial of AXS-05 for the treatment of AD agitation. We may elect to conduct interim analyses for our other clinical trials. Interim results of a clinical trial do not necessarily predict final results, and interim results may result in early stoppage of our clinical trials for futility or modifications to our clinical trials, including the addition of additional subjects. Further, our product candidates may not receive regulatory approval even if they are successful in clinical trials.

If approved for marketing by applicable regulatory authorities, our ability to generate revenues from our product candidates depend on our ability to:

- create market demand for our product candidates through our own marketing and sales activities, and any other arrangements to promote these product candidates that we may otherwise establish;
- receive regulatory approval for claims that are necessary or desirable for successful marketing;
- hire, train, and deploy a sales force to commercialize our product candidates;
- manufacture (or have manufactured by third parties) our product candidates in sufficient quantities and at acceptable quality and manufacturing cost to meet commercial demand at launch and thereafter;
- establish and maintain agreements with wholesalers, distributors, and group purchasing organizations on commercially reasonable terms;
- create partnerships with, or offer licenses to, third parties to promote and sell our product candidates in foreign markets where we receive marketing approval;
- maintain patent and trade secret protection and regulatory exclusivity for our product candidates;
- launch commercial sales of our product candidates, whether alone or in collaboration with others;
- achieve market acceptance of our product candidates by patients, the medical community, and government and private third-party payors;
- achieve appropriate reimbursement for our product candidates;
- effectively compete with other therapies; and
- maintain a continued acceptable safety profile of our product candidates following launch.

Potential conflicts of interest exist with respect to the intellectual property rights that we license from an entity owned by our Chief Executive Officer and Chairman of the Board, and it is possible that our interests and their interests may diverge.

In 2012, we entered into three exclusive license agreements with Antecip, an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which we were granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the development of certain of the Company's then current product candidates. The patents licensed from Antecip include certain intellectual property pertaining to the Company's Auvelity product / AXS-05 portfolio product. Although Dr. Tabuteau dedicates all of his working time to us, because Antecip is an inactive intellectual property holding company, he may face potential conflicts of interest regarding these licensing transactions as a result of his ownership of Antecip. The license agreements provide that, subject to the reasonable consent of Antecip, we have the right to control the prosecution or defense, as the case may require, of a patent infringement claim involving the licensed intellectual property. Our interests with respect to pleadings and settlements in such cases may be at odds with those of Antecip. If there is a dispute between us and Antecip, Dr. Tabuteau will have a conflict of interest because he may, at the time of a prospective dispute, simultaneously have a financial interest in and owe a fiduciary duty to Antecip and simultaneously have a financial interest in and owe a fiduciary duty to us. For example, if a contractual dispute arises between us and Antecip under any of the license agreements we have with Antecip, Dr. Tabuteau may be in a position where he would benefit if Antecip prevails, to the detriment of our business or our investors, even though he is an officer and director of our company, because he is the sole owner of Antecip. Similarly, if we have a claim of any kind against Antecip, Dr. Tabuteau may be, even as our Chief Executive Officer and Chairman of the Board, reluctant to assert a claim by us against Antecip because of his financial interest in Antecip. We cannot assure you that any conflicts will be resolved in our favor, and as a result, our business could be impeded or materially harmed.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both its regulatory approval and commercialization. As such, we are currently primarily focused on the development of solriamfetol for additional indications, AXS-05 for the treatment of agitation associated with AD and smoking cessation, AXS-12 for the treatment of narcolepsy, and AXS-14 for the treatment of fibromyalgia. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. Additionally, as more fully described in "Business—Material License Agreements," we are required to pay to an entity owned by our Chief Executive Officer and Chairman of the Board certain royalty payments related to the sales of the Company's Auvelity product / AXS-05 portfolio product, as well as two product candidates that are not currently in active development. This may influence management's decision concerning which product candidates or indications to pursue and/or the manner in which our products are commercialized. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing, or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Our future growth may depend on our ability to identify and develop product candidates, and if we do not successfully identify and develop product candidates or integrate them into our operations, we may have limited growth opportunities.

A component of our business strategy is to continue to develop a pipeline of product candidates by developing products that we believe are a strategic fit with our focus on CNS therapies. However, these business activities may entail numerous operational and financial risks, including:

- difficulty or inability to secure financing to fund business activities for such development;
- disruption of our business and diversion of our management's time and attention;
- higher than expected development costs;
- exposure to unknown liabilities;
- difficulty in managing multiple product development programs; and
- inability to successfully develop new products or clinical failure.

For instance, our prior efforts have resulted in our decision not to further develop certain product candidates that, at one time, appeared to be promising. Likewise, we received a CRL from the FDA relating to the Company's Symbravo product in 2022 (we have since obtained approval for Symbravo). Moreover, we may devote resources to potential development that are never completed, or we may fail to realize the anticipated benefits of such efforts. If we do not successfully develop and commercialize product candidates, we may not be able to obtain revenues from such product candidates in future periods.

If safety and efficacy data for our product candidates, a reference drug, or published literature does not satisfactorily demonstrate safety and efficacy to the FDA, or if the FDA and other regulators do not permit us to rely on the data of a reference drug or published literature, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We are not permitted to commercialize, market, promote, or sell any product candidate in the United States without obtaining marketing approval from the FDA. In the EU, we are not permitted to commercialize, market, promote, or sell any product candidate without obtaining marketing approval from the EC or national competent authorities at the EU member state level.

In the United States, we currently plan to, at least initially, seek approval of some of our product candidates using the 505(b)(2) pathway. These 505(b)(2) product candidates include additional indications for AXS-05. The FDA interprets Section 505(b)(2) of the FDCA for purposes of approving an NDA, to permit the applicant to rely, in part, upon published literature or the FDA's previous findings of safety and efficacy for an approved product. The FDA, though, requires companies to perform additional clinical trials or preclinical studies to support any deviation from the previously approved product and to support reliance on the FDA's prior findings of safety and efficacy or published literature.

Under the 505(b)(2) pathway, the FDA may approve our product candidates for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought pursuant to the Section 505(b)(2) process. The label, however, may require all or some of the limitations, contraindications, warnings, or precautions included in the reference product's label, including a box warning (commonly referred to as a "black box warning"), or may require additional limitations, contraindications, warnings, or precautions, including class-wide warnings. For instance, antidepressants, including Auvelity, include a class-wide black box warning regarding the increased risk of suicidal thoughts and behavior.

In addition, because we plan to file certain product candidates under an NDA submitted pursuant to 505(b)(2), we will rely, at least in part, upon a reference drug and published literature. For example, we have and/or intend to rely on third-party studies in the published literature as well as FDA findings of safety and efficacy for approved drug products containing the same active molecules in AXS-05. If the FDA disagrees with our conclusions regarding the appropriateness of our reliance on a reference drug or published literature, we could be required to conduct additional clinical trials or other studies to support our NDA, which could lead to unanticipated costs and delays or to the termination of our development program. If we are unable to obtain approval for our pharmaceutical formulations through the 505(b)(2) NDA process, we may be required to pursue the more expensive and time consuming 505(b)(1) approval process, which consists of full reports of investigations of safety and effectiveness conducted by or for the applicant. In addition, because we have submitted NDAs for AXS-05 and AXS-07 pursuant to the 505(b)(2) process, we have not conducted certain additional clinical trials for these product candidates and, as such, we will have less experience with actual testing of these product candidates.

There may also be circumstances under which the FDA would not allow us to pursue a 505(b)(2) application. For instance, should the FDA approve a pharmaceutically equivalent product to our product candidates before we obtain approval, we would no longer be able to use the 505(b)(2) pathway. In that case, it is the FDA's policy that the appropriate submission would be an ANDA, for a generic version of the approved product. We may, however, not be able to immediately submit an ANDA or have an ANDA approval made effective, as we could be blocked by others' periods of patent and regulatory exclusivity protection.

Notwithstanding the approval of a number of products by the FDA under 505(b)(2) over the last few years, pharmaceutical companies and others have objected to the FDA's interpretation of Section 505(b)(2). If the FDA's interpretation of Section 505(b)(2) is successfully challenged, the FDA may change its policies and practices with respect to Section 505(b)(2) regulatory approvals, which could delay or even prevent the FDA from approving any NDA that we submit pursuant to the 505(b)(2) process. Moreover, our inability to pursue a 505(b)(2) application could result in new competitive products reaching the market more quickly than our product candidates, which could hurt our competitive position and our business prospects.

The regulatory approval timelines and processes of the FDA and comparable foreign authorities are lengthy, time consuming, and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we will not be able to commercialize our product candidates as expected, and our ability to generate revenue will be materially impaired.

The timeline for review and time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities and the availability and prioritization of regulatory agency resources. The timeline for regulatory approval can be affected by a variety of factors, including budget and funding levels, agency staffing, and statutory, regulatory, and policy changes. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development, vary among jurisdictions, and/or require us to amend our clinical trial protocols or conduct additional studies that require regulatory or IRB approval, or otherwise cause delays in the approval or rejection of an application. To date, we have submitted two NDAs to the FDA and have obtained regulatory approval for both of our product candidates, Auvelity and Symbravo. It is possible that none of our other existing product candidates, or any product candidates we may seek to develop in the future, will ever obtain regulatory approval. Any delay in obtaining or failure to obtain required approvals or uncertainty in the timing of regulatory action could materially adversely impact our development efforts and affect our ability or that of any of our collaborators to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

Our products 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 comprehensive regulation by the FDA and other regulatory agencies in the United States, and by the EMA and/or national competent authorities in Europe, and similar regulatory authorities outside the United States and Europe. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have limited experience in filing and supporting the applications necessary to gain marketing approvals and rely on third party contract research organizations, or CROs, and consultants to assist us in this 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 for that indication and the submission of information about the product manufacturing process to, and inspection of manufacturing facilities and clinical trial sites by, the regulatory authorities.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies; our product candidates' mechanism of action; studies conducted by third parties in different patient populations, using different products, or using different study designs; and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. Preclinical studies may also reveal unfavorable product candidate characteristics, including safety concerns. A number of companies in the pharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Our future clinical trial results may not be successful. Moreover, should there be a flaw in a clinical trial, it may not become apparent until the clinical trial is well advanced.

We may also experience numerous unforeseen events during, or as a result of, clinical trials and in the course of our preparation, submission, and review of NDA filings that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators or IRBs may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site or amend trial protocols;

- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites and our CROs;

- clinical trials of our product candidates may produce negative or inconclusive results, or our studies may fail to reach the necessary level of statistical or clinical significance, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;

- interim analyses may result in our clinical trials being discontinued for safety or futility reasons or may result in modifications to our clinical trials that prolong the trials or make them difficult and more expensive to complete, such as increases in the number of subjects;

- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, or participants may drop out of these clinical trials at a higher rate than we anticipate;

- our third-party contractors may fail to comply with regulatory requirements or the clinical trial protocol, or meet their contractual obligations to us in a timely manner, or at all, or we may be required to engage in additional clinical trial site monitoring;

- we, the regulators, or IRBs may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks, undesirable side effects, or other unexpected characteristics of the product candidate, or due to findings of undesirable effects caused by a chemically or mechanistically similar drug or drug candidate. We may also discontinue clinical research and programs due to changing business priorities;

- changes in marketing approval policies during the development period rendering our data insufficient to obtain marketing approval;

- changes in or the enactment of additional statutes or regulations;

- changes in regulatory review for each submitted product application;

- the cost of clinical trials of our product candidates may be greater than we anticipate, or we may have insufficient funds for a clinical trial or to pay the substantial user fees required by the FDA upon the filing of an NDA;

- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;

- we may decide, or regulators may require us, to conduct additional clinical trials, analyses, reports, data, or preclinical/nonclinical studies than we currently plan, or we may abandon product development programs. For instance, although we believe that we are able to rely on the Phase 2 CONCERT trial and SYMPHONY trial to support an NDA for AXS-12 for the treatment of cataplexy and narcolepsy and the completed Phase 2 trial and Phase 3 trial to support an NDA for AXS-14 for the management of fibromyalgia, the FDA could still require additional studies to support the approval of an NDA for these product candidates. The outcome of our studies may further necessitate additional clinical or preclinical work;

- we may fail to reach an agreement with regulators regarding the scope or design of our clinical trials;

- we may have delays in adding new investigators or clinical trial sites, or we may experience a withdrawal of clinical trial sites;

- patients that enroll in our studies may misrepresent their eligibility or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the study or clinical trial, increase the needed enrollment size for the study or clinical trial, or extend the study's or clinical trial's duration;

- there may be regulatory questions regarding interpretations of data and results, or new information may emerge regarding our product candidates;

- the FDA or comparable foreign regulatory authorities may disagree with our study design or our interpretation of data from preclinical studies and clinical trials or find that a product candidate's benefits do not outweigh its safety risks. For instance, in our communications with the FDA, the FDA has raised questions and had comments regarding our preclinical studies and clinical trials, such as comments on the acceptability of the proposed trial designs for our product candidates, the number of patients planned for our studies, our data analysis plans, the species and doses used in our preclinical studies, and the results of our preclinical studies;

- the FDA or comparable foreign regulatory authorities may disagree with our belief that certain product attributes are advantageous or may require further study of product attributes that are different than our reference listed drugs. Pharmacokinetic differences between our product candidates and the reference listed drugs, may also make bridging studies more difficult or may prevent us from using the 505(b)(2) pathway. If we are prevented from using the 505(b)(2) pathway, we will need to use the more time consuming and expensive NDA pathway to receive product approval;

- the FDA or comparable foreign regulatory authorities may not accept data from studies with clinical trial sites in foreign countries;

- the FDA or comparable foreign regulatory authorities may disagree with our intended indications;

- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or our manufacturing facilities for clinical and future commercial supplies;

- in connection with the CMC data necessary for our NDA filing and approval, we will need to conduct stability studies and provide stability data to establish appropriate retest or expiration dating periods;

- our product candidates may not demonstrate sufficient long-term stability to support an NDA filing or obtain approval, or the product shelf life may be limited by stability results;

- there may be delays in the FDA's ability to conduct necessary Pre-Approval Inspections, or PAIs, and more generally the FDA or comparable foreign regulatory authorities may take longer than we anticipate to make a decision on our product candidates; and

- we may not be able to demonstrate that a product candidate provides an advantage over current standards of care or current or future competitive therapies in development.

Moreover, if we are required to conduct additional clinical trials or other testing of our product candidates beyond that which we currently contemplate, if we are unable to successfully complete clinical trials or other testing of our product candidates, if the results of these trials or tests are not positive, or are only modestly positive, or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our product candidates;

- not obtain marketing approval at all;

- obtain approval for indications or patient populations that are not as broad as intended or desired or are not covered by our intellectual property;

- obtain approval with labeling that includes significant use or distribution restrictions, including restrictions on the intended patient population, or safety warnings, including boxed warnings, contraindications, and precautions, or may not include label statements necessary or desirable for successful commercialization;

- be subject to additional post-marketing testing and surveillance requirements, including REMS; or
- have the product removed from the market after obtaining marketing approval.

In addition, the FDA's and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our product development plans may be impacted. For example, in December 2022, with the passage of the Food and Drug Omnibus Reform Act (FDORA), Congress required sponsors to develop and submit a diversity action plan for each phase 3 clinical trial or any other "pivotal study" of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late-stage clinical trials of FDA-regulated products. Specifically, diversity action plans must include the sponsor's goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In terms of the compliance deadline, the requirement to submit a diversity action plan applies to clinical studies for which enrollment begins 180 days after the final guidance is published, which was originally anticipated to occur in June 2025. In January 2025, the previously-published draft guidance was removed from the FDA website, which may impact the eventual publication date of the final guidance, and as a result, may delay the compliance deadline.

Our product candidate development costs will also increase if we experience delays in testing or approvals and we may not have sufficient funding to complete the testing and approval process for any of our product candidates. We may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We do not know whether any additional preclinical tests or clinical trials will be required, will begin as planned, will need to be restructured, or will be completed on schedule, or at all. Significant delays relating to any preclinical studies or clinical trials also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of our collaborators, to bring products to market before we do and impair our ability to successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that cause, or lead to, such delays may ultimately lead to the denial of marketing approval of any of our product candidates. If any of this occurs, our business, financial condition, results of operations, and prospects may be materially harmed.

Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical studies, clinical trials, or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit, or prevent marketing approval of a product candidate. During the course of review, the FDA may also request or require additional CMC, or other data and information, and the development and provision of these data and information may be time consuming and expensive. For example, in the CRL with respect to our NDA for Symbravo, the FDA noted the need for additional CMC data. Symbravo was subsequently approved by the FDA. Furthermore, there is the possibility that the FDA or comparable foreign regulatory authorities have not previously reviewed product candidates for the indications we are pursuing, such as AD agitation or smoking cessation. As a result, we may experience delays in regulatory approval due to uncertainties in the approval process.

If we experience delays in obtaining approval, if we fail to obtain approval of a product candidate or if the label for a product candidate does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate, the commercial prospects for such product candidate may be harmed and our ability to generate revenues from that product candidate will be materially impaired. Furthermore, there is the possibility that the FDA or comparable foreign regulatory authorities have not previously reviewed product candidates for the indications we are pursuing, such as AD agitation or smoking cessation. As a result, we may experience delays in regulatory approval due to uncertainties in the approval process.

If we cannot demonstrate an acceptable safety and toxicity profile for our product candidates, we will not be able to continue our clinical trials of or obtain approval for those product candidates.

In order to obtain approval of a product candidate we must demonstrate safety in various nonclinical tests (including, for example, carcinogenicity studies, drug-drug interaction studies, and toxicity studies), in addition to human clinical trials. At the time of initiating human clinical trials, we may not have conducted or may not conduct all the types of nonclinical testing ultimately required by regulatory authorities, or future nonclinical tests may indicate safety concerns regarding our product candidates. Nonclinical testing and clinical testing are both expensive and time-consuming and have uncertain outcomes. Even if initial tests appear favorable, later testing may have unfavorable results. We may experience numerous unforeseen events during, or as a result of, the testing process, which could delay or prevent our ability to develop or commercialize our product candidates, including:

- our preclinical or nonclinical testing may produce inconclusive or negative safety results, which may require us to conduct additional nonclinical testing or to abandon product candidates;
- our product candidates may have unfavorable pharmacology or toxicity characteristics or suggest possible drug-drug interaction;
- our product candidates may cause undesirable side effects; and
- the FDA or other regulatory authorities may determine that additional safety testing is required.

Any such events would increase our costs and could delay or prevent our ability to commercialize our product candidates, which could adversely impact our business, financial condition and results of operation.

The FDA may determine that any of our current or future product candidates have undesirable side effects that could delay or prevent their regulatory approval or commercialization.

Undesirable side effects caused by our product candidates could cause us, IRBs, and other reviewing entities or regulatory authorities to interrupt, delay, or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. For example, if concerns are raised regarding the safety of a new drug as a result of undesirable side effects identified during clinical or preclinical testing, the FDA may order us to cease further development, decline to approve the drug, or issue a letter requesting additional data or information prior to making a final decision regarding whether or not to approve the drug.

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 any of our current or future product candidates could also result in denial of regulatory approval by the FDA or other comparable foreign authorities for any or all targeted indications or the inclusion of unfavorable information in our product labeling, such as limitations on the indicated uses for which the products may be marketed or distributed, a label with significant safety warnings, including boxed warnings, contraindications, and precautions, a label without statements necessary or desirable for successful commercialization, or may result in requirements for costly post-marketing testing and surveillance, or other requirements, including REMS, to monitor the safety or efficacy of the products, and in turn prevent us from commercializing and generating revenues from the sale of any of our current or future product candidates.

Based on the side effects disclosed in the EMA required product label for marketed drugs that contain the same active molecule as our product candidates, AXS-12 and AXS-14 may result in decreased appetite, insomnia, agitation, anxiety, dizziness, headache, paresthesia, akathisia, dysgeusia, accommodation disorder, mydriasis, glaucoma, vertigo, tachycardia, palpitations, vasodilation, hypotension, hypertension, dry mouth, vomiting, hyperhidrosis, rash, sensation of incomplete bladder emptying, urinary tract infection, dysuria, urinary retention, erectile dysfunction, ejaculatory pain, ejaculatory delay, chills, or other adverse events or potential adverse events reported or discussed in the product labels for reboxetine containing products, including Edronax®.

Known side effects for Auvelity, Sunosi, and Symbravo are described on the approved labels for those products. In relation to further development efforts with respect to these compounds, different patient populations may react to these compounds differently. For example, AD agitation patients in the case of AXS-05 or ADHD patients in the case of solriamfetol may experience different side effects than patients taking these products for their currently approved indications. This is particularly true where different dosing, formulations or methods of administration are implicated.

If any of our other product candidates are associated with serious adverse events or undesirable side effects or have properties that are unexpected, we may need to abandon development or limit development of that product candidate to certain 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. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may significantly harm our business, financial condition, results of operations, and prospects.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue conducting clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the United States. Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment is affected by other factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the eligibility criteria for, and design of, the clinical trial in question, including factors such as frequency of required assessments, length of the study, and ongoing monitoring requirements;
- the perceived risks and benefits of the product candidate under study, including the potential advantages or disadvantages of the product candidate being studied in relation to other available therapies;
- competition in recruiting and enrolling patients in clinical trials;
- the efforts to facilitate timely enrollment in clinical trials;
- the patient referral practices of physicians;
- effectiveness of publicity created by clinical trial sites regarding the trial;
- patients' ability to comply with the specific instructions related to the trial protocol, proper documentation, and use of the drug product;
- inability to obtain or maintain patient informed consents;
- risk that enrolled patients will drop out before completion;
- the ability to identify patients for enrollment and maintain a sufficient level of patient participants in our clinical studies;
- the ability to monitor patients adequately during and after treatment; and

- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays which would cause us to miss our projected timelines and could require us to abandon one or more clinical trials altogether. For instance, because we are seeking regulatory approval for certain indications that may have a narrow or small patient population, it may be difficult to find patients eligible to participate in our clinical studies at a sufficient rate or in a sufficient quantity. We may be required by the FDA to modify the entry criteria for our planned Phase 3 clinical trials and these changes may make it more difficult to enroll patients in our clinical trials. Moreover, patients in our clinical trials, especially patients in our control groups, may be at risk for dropping out of our studies if they are not experiencing relief of their symptoms. A significant number of withdrawn patients would compromise the quality of our data.

Enrollment delays or slower periods of enrollment in our clinical trials may result in increased development costs for our product candidates, or the inability to complete development of our product candidates, which would cause the value of our company to decline, limit our ability to obtain additional financing, and materially impair our ability to generate revenues.

Development of combination product candidates may present more or different challenges than development of single agent product candidates.

Certain product candidates of ours, including AXS-05, are combination therapies. A combination therapy is a single drug product that consists of two or more active ingredients, with each component making a contribution to the claimed effect of the drug. The development of combination drugs may be more complex than the development of single agent products and generally requires that sponsors demonstrate the contribution of each component to the claimed effect and the safety and efficacy of the product as a whole. This requirement may make the design and conduct of clinical trials more complex, requiring more clinical trial subjects. We also may not be able to meet the FDA's approval standards required for combination products. The FDA's requirements concerning combination products may change in the future. Moreover, the applicable requirements for approval may differ from country to country.

Changes in product candidate manufacturing or formulation may result in additional costs or delay.

As product candidates are developed through preclinical studies to late-stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. For instance, as we begin scale-up efforts for commercial-size manufacturing batches, formulation changes may be necessary to improve tablet robustness. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the altered materials. Such changes may also require additional testing, FDA notification, or FDA approval. This could delay completion of clinical trials; require the conduct of bridging clinical trials or studies, or the repetition of one or more clinical trials; increase clinical trial costs; delay approval of our product candidates; and jeopardize our ability to commence product sales and generate revenue.

Failure to obtain marketing approval in international jurisdictions would prevent our products from being marketed abroad.

In order to market and sell our products in the EU, and many other jurisdictions, we or our third-party collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our ability to obtain approval elsewhere. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Although Breakthrough Therapy, Fast Track, and other designations are designed to expedite the development and review of drugs, they may not ultimately lead to a faster approval process or faster development of regulatory review, and they will not increase the likelihood that our product candidates will receive marketing approval, for example, Breakthrough Therapy designation by the FDA for AXS-05 for the treatment of AD agitation.

We have received a Fast Track product designation for AXS-05 for both the treatment of TRD as well as for the treatment of AD agitation, and we may seek Fast Track designation for other of our current or future product candidates. The FDA may designate a product for Fast Track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For Fast Track products, sponsors may have greater interactions with the FDA, and the FDA may initiate review of sections of a Fast Track product's application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information, and the sponsor must pay applicable user fees.

We also received Breakthrough Therapy designation for AXS-05 for both the treatment of MDD and the treatment of AD agitation, and we may seek Breakthrough Therapy designation for other current or future product candidates. A Breakthrough Therapy is defined as a product candidate that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For product candidates that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Breakthrough Therapy designation also allows the sponsor to request a Priority Review or file sections of the NDA on an ongoing basis for rolling review where the FDA may consider beginning review portions of a marketing application before the full submission is complete. Product candidates designated as Breakthrough Therapies by the FDA are also eligible for Priority Review if supported by clinical data at the time of the submission of the NDA.

Breakthrough Therapy or Fast Track designation is within the discretion of the FDA. The receipt of a Breakthrough Therapy or Fast Track designation for a product candidate may not ultimately result in a faster development process or review, and it does not in any way assure approval of product candidates by the FDA. In addition, the FDA may later decide to rescind the Breakthrough Therapy or Fast Track designation for one or more of our applicable product candidates if such product candidates no longer meet the conditions for qualification of this program. For example, we were initially granted Breakthrough Therapy designation for AXS-12 for the treatment of cataplexy in patients with narcolepsy in August 2020. In July 2021, the FDA rescinded our Breakthrough Therapy designation due to the FDA approving an additional drug product for the treatment of cataplexy in narcolepsy.

Regulatory approval is limited by the FDA or comparable foreign regulatory authorities to those specific indications and conditions for which clinical safety and efficacy have been demonstrated, and we may be subject to fines, penalties, injunctions, or other enforcement actions if we are determined to be promoting the use of our products for unapproved or "off-label" uses, resulting in damage to our reputation and business.

We, and any of our collaborators, must comply with requirements concerning advertising and promotion for any of our products for which we or they obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and continuing review by the FDA, Department of Justice, HHS's OIG, state attorneys general, members of Congress, and the public. When the FDA or comparable foreign regulatory authorities issue regulatory approval for a product candidate, the regulatory approval is limited to those specific uses and indications for which a product is approved. If we are not able to obtain FDA or comparable foreign regulatory authorities' approval for any desired uses or indications for our products and product candidates, we may not market or promote our products for those indications and uses, referred to as off-label uses, and our business may be adversely affected. We further must be able to sufficiently substantiate any claims that we make for our products including claims comparing our products to other companies' products.

While physicians may choose to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those tested in clinical studies and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications and uses that are not specifically approved by the FDA or comparable foreign regulatory authorities. 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 and in many other major markets do not generally restrict or regulate the behavior of physicians in their choice of treatment within the practice of medicine. Regulatory authorities do, however, restrict communications by pharmaceutical companies concerning off-label use.

If we are found to have impermissibly promoted any of our products, we may become subject to significant liability and government fines. The FDA and other agencies actively enforce the laws and regulations regarding product promotion, particularly those prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted a product may be subject to significant sanctions. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees of permanent injunctions under which specified promotional conduct is changed or curtailed. Thus, we and any of our collaborators will not be able to promote any products we develop for indications or uses for which they are not approved.

In the United States, engaging in the impermissible promotion of our products, following approval, for off-label uses can also subject us to false claims and other litigation under federal and state statutes, including fraud and abuse and consumer protection laws, which can lead to civil and criminal penalties and fines, agreements with governmental authorities that materially restrict the manner in which we promote or distribute drug products and do business through, for example, corporate integrity agreements, suspension or exclusion from participation in federal and state healthcare programs, and debarment from government contracts and refusal of future orders under existing contracts. Recent court decisions have impacted the FDA's enforcement activity regarding off-label promotion in light of First Amendment considerations; however, there are still significant risks in this area in part due to the potential FCA exposure. The FCA allows any individual to bring a lawsuit against a pharmaceutical company on behalf of the federal government alleging submission of false or fraudulent claims or causing others to present such false or fraudulent claims, for payment by a federal program such as Medicare or Medicaid. If the government decides to intervene and prevails in the qui tam lawsuit, the individual will share in the proceeds from any fines or settlement funds. If the government declines to intervene, the individual may pursue the case alone. Under the FCA, a penalty may be imposed for each false claim, for example, a claim for payment for each prescription for the product, and, when aggregated, these penalties often total millions of dollars and incentivize qui tam lawsuits. These FCA lawsuits against pharmaceutical companies have increased significantly in volume and breadth, leading to several substantial civil and criminal settlements, pertaining to certain sales practices and promoting off-label drug uses. This growth in litigation has increased the risk that a pharmaceutical company will have to defend a false claim action; pay settlement fines or restitution, as well as criminal and civil penalties; agree to comply with burdensome reporting and compliance obligations; and be excluded from Medicare, Medicaid, or other federal and state healthcare programs. If we or our collaborators do not lawfully promote our approved products, if any, we may become subject to such litigation and other actions and, if we do not successfully defend against such actions, those actions may have a material adverse effect on our business, financial condition, results of operations, and prospects.

In the United States, the distribution of product samples to physicians must further comply with the requirements of the U.S. PDMA. If the FDA determines that our promotional materials or activities violate its regulations and policies pertaining to product promotion, it could request that we modify our promotional materials or activities or subject us to regulatory or other enforcement actions, including issuance of warning letters or untitled letters, suspension or withdrawal of an approved product from the market, requests for recalls, payment of civil fines, disgorgement of money, imposition of operating restrictions, injunctions, or criminal prosecution. These regulatory and enforcement actions could significantly harm our business, financial condition, results of operations, and prospects.

We are, and will continue to be subject to, ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, any of our products, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

Our product(s) are subject to extensive and ongoing requirements of and review by the FDA and other regulatory authorities, including requirements related to the manufacturing processes, post-approval clinical data, labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising, marketing, and promotional activities for such product. These requirements further include submissions of safety and other post-marketing information, including manufacturing deviations and reports; registration and listing requirements; the payment of annual program fees for our products; continued compliance with 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; and GCP, for any clinical trials that we conduct post-approval.

We and any of our collaborators, including our contract manufacturers, could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMP and GCP. Application holders must further notify the FDA, and depending on the nature of the change, obtain FDA pre-approval for product and manufacturing changes. Application fees may apply to certain changes.

In addition, later discovery of previously unknown adverse events or that the drug is less effective than previously thought or other problems with our products, manufacturers, or manufacturing processes, or failure to comply with regulatory requirements both before and after approval, may yield various results, including:

- restrictions on manufacturing or distribution, or marketing of such products;
- restrictions on the labeling, including required additional warnings, such as black box warnings, contraindications, precautions, and restrictions on the approved indication or use;
- modifications to promotional pieces;
- requirements to conduct post-marketing studies or clinical trials;
- clinical holds or termination of clinical trials;
- requirements to establish or modify a REMS or a comparable foreign authority may require that we establish or modify a similar strategy, that may, for instance, require us to create or modify a medication guide outlining the risks of the previously unidentified side effects for distribution to patients, or restrict distribution of the product, if and when approved, and impose burdensome implementation requirements on us;
- changes to the way the drug is administered;
- liability for harm caused to patients or subjects;
- reputational harm;
- the drug becoming less competitive;
- warning or untitled letters;
- suspension of marketing or withdrawal of the products from the market;
- regulatory authority issuance of safety alerts, Dear Healthcare Provider letters, press releases, or other communications containing warnings or other safety information about the drug;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, damages, restitution, or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure or detention;
- FDA debarment, debarment from government contracts, and refusal of future orders under existing contracts, exclusion from federal healthcare programs, consent decrees, or corporate integrity agreements; or
- injunctions or the imposition of civil or criminal penalties, including imprisonment.

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product, or could substantially increase the costs and expenses of commercializing such product, which in turn could delay or prevent us from generating significant revenues from its sale. Any of these events could further have other material and adverse effects on our operations and business and could adversely impact our stock price and could significantly harm our business, financial condition, results of operations, and prospects.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit, or delay regulatory approval of our product candidates or that could impose additional regulatory obligations on our products. 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 and be subject to regulatory enforcement action.

In addition, there is a great degree of uncertainty regarding how recent U.S. Supreme Court decisions, including *Loper Bright Enterprises v. Raimondo*, 603 U.S. 369 (2024) and *Corner Post, Inc. v. Board of Governors of the Federal Reserve System*, 603 U.S. 799 (2024), will impact the FDA's enforcement and decision-making authority. *Loper Bright* explicitly overturned *Chevron* deference, which previously gave judicial deference to administrative action by agencies in the executive branch. Furthermore, the Supreme Court's decision in *Corner Post* may result in challenges to FDA decisions by new litigants long into the future. These decisions could result in additional legal challenges to regulations and guidance issued by federal agencies, including the FDA, on which we rely. Any such legal challenges, if successful, could have a material impact on our business. Additionally, the *Loper* decision may result in increased regulatory uncertainty, inconsistent judicial interpretations, and could impact various aspects of the agency rulemaking process, any of which could adversely impact our business and operations. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action or as a result of legal challenges, either in the United States or abroad. 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, our business could be materially harmed.

Should any of the above actions take place, they could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

A variety of risks associated with international operations could materially adversely affect our business.

We are, and may become party to further agreements, pursuant to which we out-license our products outside of the United States. The Company also currently markets Sunosi in Canada. We expect that we will be subject to additional risks related to entering into international business relationships, including:

- different regulatory requirements for approval of drugs in foreign countries;
- the potential for so-called parallel importing, particularly within Europe, which is what happens when a local seller, faced with high or higher local prices, opts to import goods from a foreign market (with low or lower prices) rather than buying them locally with EU laws supporting such "free movement of goods" within the EU;
- stricter harmonized EU rules on data privacy particularly in relation to personal data, including health data, than is the case in the United States which are being further toughened with the EU General Data Protection Regulation, or the GDPR, which became enforceable beginning May 25, 2018;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- unexpected changes in tariffs, trade barriers, and regulatory requirements and in the health care policies of foreign jurisdictions;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;

- compliance with tax, employment, immigration, and labor laws for employees living or traveling abroad;
- foreign taxes, including withholding of payroll taxes;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- difficulties staffing and managing foreign operations;
- workforce uncertainty in countries where labor unrest is more common than in the United States and worker rights tend to be stronger;
- costs of compliance with U.S. laws and regulations for foreign operations, including the FCPA or comparable foreign regulations, and the risks and costs of noncompliance;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods, and fires.

These and other risks associated with our international operations may materially adversely affect our ability to attain or maintain profitable operations.

We are exposed to market risk from fluctuations in currency exchange rates and interest rates.

We operate in multiple jurisdictions, and virtually all sales are denominated in currencies of the local jurisdiction. Additionally, we have entered and may enter into business development transactions, borrowings, or other financial transactions that may give rise to currency and interest rate exposure.

Since we cannot, with certainty, foresee and mitigate against such adverse changes, fluctuations in currency exchange rates, interest rates, and inflation could negatively affect our business, cash flow, results of operations, financial condition, and prospects.

In order to mitigate against the adverse impact of these market fluctuations, we may from time to time enter into hedging agreements. While hedging agreements, such as currency options and forwards and interest rate swaps, may limit some of the exposure to exchange rate and interest rate fluctuations, such attempts to mitigate these risks may be costly and not always successful.

We will need to obtain FDA approval (and that of comparable foreign regulatory authorities) of any proposed product names, and any failure or delay associated with such approval may adversely affect our business.

Any name 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 names, including an evaluation of the potential for confusion with other product names. The FDA may also object to a product name if it believes the name inappropriately implies medical claims or contributes to an overstatement of efficacy. If the FDA objects to any of our proposed product names, we may be required to adopt alternative names for our product candidates. If we adopt alternative names, we would lose the benefit of any existing trademark applications for such product candidate and may be required to expend significant additional resources in an effort to identify a suitable product 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 commercialize our product candidates.

RISKS RELATED TO THE COMMERCIALIZATION OF OUR PRODUCTS

We face significant competition from other pharmaceutical and biotechnology companies, academic institutions, government agencies, and other research organizations. Our operating results will suffer if we fail to compete effectively.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current products and product candidates and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of CNS disorders. Potential competitors also include academic institutions, government agencies, and other public and private research organizations that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization.

Specifically, there are a large number of companies developing or marketing therapies for CNS disorders, including many major pharmaceutical and biotechnology companies. Among the companies that currently market or are developing therapies that, if approved, our product candidates would potentially compete with include: AbbVie Inc.; Amgen Inc.; Avadel Pharmaceuticals plc; Biogen Inc.; Eli Lilly and Company; H. Lundbeck A/S; Harmony Biosciences LLC; Intra-Cellular Therapies, Inc.; Janssen; Jazz; Otsuka Pharmaceutical Co. Ltd.; Pfizer; and Takeda Pharmaceutical Company Limited.

Our commercial opportunities could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, more convenient, or less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payors seeking to encourage the use of generic products or therapeutically similar lower cost brands. If our product candidates achieve marketing approval, we expect that they will be priced at a significant premium over competitive generic products, which would further impact our commercialization efforts.

Generic forms of the active ingredients of our product candidates, including dextromethorphan, bupropion, meloxicam, rizatriptan, and reboxetine, are available in the United States and abroad and could be used off-label. Any such off-label use could adversely affect our profitability and have a negative effect on our operating results and financial condition. For example, even though meloxicam is not currently approved for the treatment of acute migraine, we would not be able to prevent a physician from prescribing it for such treatment. Nor could we prevent a payor from offering favorable coverage for such product and disadvantaging our product candidates, even if the generics would be used off-label.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with, or acquisition by large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If the FDA or comparable foreign regulatory authorities approve generic or similar versions of any of our products that receive marketing approval, or such authorities do not grant our products appropriate periods of exclusivity before approving generic or similar versions of our products, the sales of our products could be adversely affected.

Once an NDA is approved, the covered product becomes a "reference listed drug" in the FDA's Orange Book. Manufacturers may seek approval of generic versions of reference listed drugs through submission of ANDAs in the United States. In support of an ANDA, a generic manufacturer need not conduct full clinical studies. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use or labeling, among other commonalities, as the reference listed drug and that the generic version is bioequivalent to the reference listed drug, meaning it is absorbed in the body at the same rate and to the same extent. For example, in February 2023, we received a paragraph IV certification notice letter from Teva providing notification to the Company that Teva has submitted an ANDA to the FDA seeking approval to manufacture, use, or sell a generic version of Auvelity. Additionally, beginning in August 2023, we received paragraph IV certification notice letters from six other pharmaceutical companies providing notification to the Company that each such filer has submitted an ANDA to the FDA seeking approval to manufacture, use, or sell a generic version of Sunosi.

Recently, the FDA and Congress have also taken steps to encourage increased generic drug competition in the market. Generic products may be significantly less costly to bring to market than the reference listed drug and companies that produce generic products are generally able to offer them at lower prices and are generally preferred by third-party payors. Thus, following the introduction of a generic drug, a significant percentage of the sales of any branded product or reference listed drug is typically lost to the generic product.

Moreover, in addition to generic competition, we could face competition from other companies seeking approval of drug products that are similar to ours using the 505(b)(2) pathway. Such applicants may be able to rely on our products, or other approved drug products or published literature to develop drug products that are similar to ours. The introduction of a drug product similar to our product candidates could expose us to increased competition.

Further, if we do not file a patent infringement lawsuit against a generic manufacturer within 45 days of receiving notice of its paragraph IV certification, the ANDA or 505(b)(2) applicant may not be subject to a 30-month stay. Litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be expensive and time consuming, may divert our management's attention from our core business, and may result in unfavorable results that could adversely impact our ability to prevent third parties from competing with our products. Accordingly, we may be subject to generic competition or competition from similar products, or may need to commence patent infringement proceedings, which would divert our resources.

Competition that our products may face from generic or similar versions of our products could materially and adversely impact our future revenue, profitability, and cash flows and substantially limit our ability to obtain a return on the investments we have made in our product candidates.

AXS-12 received Orphan Drug Designation from the FDA. However, there is no guarantee that we will receive this designation for any of our other product candidates or receive or maintain any corresponding benefits for any of our other product candidates that may receive Orphan Drug Designation in the future, including periods of exclusivity.

AXS-12 received Orphan Drug Designation from FDA for the treatment of narcolepsy. We may also seek Orphan Drug Designation for our other products, as appropriate.

Orphan Drug Designation, however, may be lost if the indications for which we develop any of our future product candidates do not meet the orphan drug criteria. Moreover, following product approval, orphan drug exclusivity may be lost if the FDA determines, among other reasons, that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition. Even if we obtain orphan drug exclusivity for any of our current or future product candidates, that exclusivity may not effectively protect the product from competition because different products can be approved for the same condition. Even after an orphan product is approved, the FDA can subsequently approve a product containing the same principal molecular features for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer or more effective or makes a major contribution to patient care.

The FDA or the EMA may grant orphan exclusivity to two different sponsors for the same compound or active molecule and for the same indication. For example, if another sponsor receives FDA approval for a reboxetine containing product for the treatment of narcolepsy before we obtain FDA approval for AXS-12 for the treatment of narcolepsy, we would be prevented from launching our product in the United States for this indication for a period of at least 7 years. If another sponsor receives EMA approval for a reboxetine containing product for the treatment of narcolepsy before we obtain EMA approval for AXS-12 for the treatment of narcolepsy, we would be prevented from launching our product in the EU for this indication for a period of at least 10 to 12 years.

The FDA may undertake a reevaluation of aspects of its orphan drug regulations and policies at any time and may possibly do so in response to a recent court decision regarding the plain meaning of the exclusivity provision of the Orphan Drug Act. We do not know if, when, or how the FDA may change the orphan drug regulations and policies, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business, financial condition, results of operations, and prospects could be harmed.

If we are unable to establish effective marketing, sales and distribution capabilities or enter into agreements with third parties to market, sell and distribute our products, we may be unable to generate significant product awareness and that lack of awareness may limit the product revenues that we generate.

We recently expanded our commercial infrastructure for the marketing, sale, and distribution of pharmaceutical products, which included the creation of a sales force to launch our commercial stage products throughout the United States. This effort requires additional compliance with a range of federal and state laws. Additionally, we currently commercialize Sunosi outside the United States. Each global market we commercialize Sunosi in has its own set of applicable laws.

We have limited experience in the marketing, sale, and distribution of pharmaceutical products, and there are significant risks involved in the building and managing of a commercial infrastructure. We have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, manage, and retain marketing and sales personnel. In the event we are unable to maintain our marketing and sales infrastructure, we may not be able to successfully commercialize any of our existing commercial stage products or future product candidates, which would limit our ability to generate revenue. Factors that may inhibit our efforts to commercialize any of our products on our own include:

- our inability to recruit, train, manage, and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or appropriately persuade adequate numbers of physicians to prescribe any of our current or future product candidates;
- our inability to effectively oversee a geographically dispersed sales and marketing team;
- the application of federal and state drug distribution and supply chain requirements to our business;

- the costs associated with training sales and marketing personnel on legal and regulatory compliance matters and monitoring their actions;

- an inability to secure adequate or any coverage and reimbursement by government and private health plans or other payers;

- the clinical indications and labeled claims for which the product is approved;

- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling;

- any distribution and use restrictions imposed by the FDA or to which we agree as part of a mandatory REMS or voluntary risk management plan;

- liability for sales or marketing personnel who fail to comply with the applicable legal and regulatory requirements;

- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and

- unforeseen costs and expenses associated with creating an independent sales and marketing organization or engaging a contract sales organization.

If additional product candidates are approved, we may incur expenses prior to product launch in expanding our sales force and compliant marketing and sales infrastructure. If a commercial launch is delayed as a result of FDA requirements or other reasons, we may incur these expenses prior to being able to realize any revenue from sales of such product candidate(s). Furthermore, our sales force and marketing teams may not be successful in commercializing any of our current or future product candidates.

If any of our products do not achieve broad market acceptance, the revenues that we generate from their sales will be limited.

Our products, and, if approved, our product candidates, may not gain acceptance among physicians, patients, third-party payors, or others in the medical community. If any of our products or product candidates, for which we obtain regulatory approval, do not gain an adequate level of market acceptance, we may not generate significant product revenues or become profitable. Market acceptance of any of our products by the medical community, patients, and third-party payors will depend on a number of factors, some of which are beyond our control. For example, physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Physicians and their patients may likewise make decisions about therapies based on cost and insurance coverage and reimbursement. Such reimbursement may be impacted by our ability to enter into single-case agreements (in the absence of a longer term agreement) with insurance companies, and the absence of any agreement or inadequate coverage or reimbursement may require patients to pay from their own funds, but the costs of our product may be prohibitive in such cases. Further, patients often acclimate to the therapy that they are currently taking. While they may switch if their physicians recommend switching products, there is no guarantee. Additionally, they may also switch therapies due to lack of reimbursement for existing therapies or for other reasons. Even if physicians prescribe our products, third-party payors may not provide coverage or may not consider them cost effective without a significant price concession, which could negatively impact our revenue. Third-party payors may also implement onerous access controls, which could further impede our efforts to effectively transition eligible patients to our therapies.

Efforts to educate the medical community and third-party payors on the benefits of our products may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues, and we may not become profitable. The degree of market acceptance of any of our products will depend on a number of factors, including:

- the efficacy of our products;
- the prevalence and severity of adverse events associated with such product;
- the clinical indications for which the product is approved and the approved claims that we may make for the product;
- limitations or warnings contained in the product's FDA-approved labeling, including potential limitations or warnings for such product candidate, that may be more restrictive than other competitive products;
- changes in the standard of care for the targeted indications for such product candidate, which could reduce the marketing impact of any claims that we could make following FDA approval, if obtained;
- the relative convenience and ease of administration of such product;
- cost of treatment versus economic and clinical benefit in relation to alternative treatments or therapies;
- the availability of adequate coverage or reimbursement by third parties, such as insurance companies and other healthcare payors, and by government healthcare programs, including Medicare and Medicaid;
- the willingness of third-party payors to prefer other products, even if not approved for our product's indication;
- the extent and strength of our marketing and distribution of such product;
- the safety, efficacy, and other potential advantages over, and availability of, alternative treatments already used or that may later be approved for any of our intended indications;
- distribution and use restrictions imposed by the FDA with respect to such product or to which we agree as part of a mandatory REMS or voluntary risk management plan;
- the timing of market introduction of such product, as well as competitive products;
- our ability to offer such product candidate for sale at competitive prices, including prices that are competitive with generic products;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the extent and strength of our third-party manufacturer and supplier support;
- the approval of other new products for the same indications;
- adverse publicity about the product or favorable publicity about competitive products; and
- potential product liability claims.

Our efforts to educate the medical community and third-party payors on the benefits of our products may require significant resources and may never be successful. Even if the medical community accepts that one of our product candidates is safe and effective for its approved indications and third-party payors provide coverage and reimbursement for the same, physicians and patients may not immediately be receptive to such product candidate and may be slow to adopt it as an accepted treatment of the approved indication or may not accept it at all. It is unlikely that any labeling approved by the FDA will contain claims that one of our product candidates is safer or more effective than competitive products or will permit us to promote such product candidate as being superior to competing products.

The potential market opportunities for our products and/or product candidates are difficult to precisely estimate. Our estimates of the potential market opportunities are predicated on many assumptions including industry knowledge and publications, third-party research reports, and other surveys. While we believe that our internal assumptions are reasonable, these assumptions involve the exercise of significant judgment on the part of our management and are inherently uncertain, and the reasonableness of these assumptions has not been assessed by an independent source. If any of the assumptions proves to be inaccurate, the actual markets for our product candidates could be smaller than our estimates of the potential market opportunities.

We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability and may have to limit our products' commercialization.

The use of any of our current or future product candidates in clinical trials, and the sale of any of our products exposes us to the risk of product liability claims. We face inherent risk of product liability related to the testing of our product candidates in human clinical trials and face an even greater risk for our commercialized products. For example, we may be sued if any products we develop allegedly cause injury or are 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. Claims could also be asserted under state consumer protection acts. Product liability claims might be brought against us by consumers, healthcare providers, or others using, administering, or selling our products. If we cannot successfully defend ourselves against these claims, we will incur substantial liabilities or be required to limit commercialization of our products. Even successful defense would require significant financial and management resources. Regardless of merit or eventual outcome, liability claims may result in loss of revenue, including from:

- decreased demand for our products;
- impairment of our business reputation or financial stability;
- costs of related litigation;
- substantial monetary awards to patients or other claimants;
- diversion of management attention;
- loss of revenues;
- withdrawal of clinical trial participants and potential termination of clinical trial sites or entire clinical programs;
- the inability to commercialize our product candidates;
- significant negative media attention;
- decrease in our stock price;
- initiation of investigations and enforcement actions by regulators; and

- product recalls, withdrawals, or labeling, marketing, or promotional restrictions.

We have obtained limited product liability insurance coverage for our products and our clinical trials. We have also obtained local policies in those foreign jurisdictions where it was appropriate. 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. 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 and our prospects.

Sunosi is a controlled substance and may be subject to U.S. federal and state controlled substance laws and regulations, and our failure to comply with these laws and regulations, or the cost of compliance with these laws and regulations, could materially and adversely affect our business, results of operations, financial condition and growth prospects.

Sunosi contains controlled substances as defined in the Federal Controlled Substances Act, or CSA. Controlled substances are subject to a number of requirements and restrictions under the CSA and implementing regulations, including certain registration, security, recordkeeping, reporting, import, export and other requirements administered by the U.S. Drug Enforcement Administration, or DEA. The DEA classifies controlled substances into five schedules: Schedule I, II, III, IV or V substances. Schedule I substances by definition have a high potential for abuse, have no currently "accepted medical use" in the U.S., lack accepted safety for use under medical supervision, and may not be prescribed, marketed or sold in the U.S. Pharmaceutical products approved for use in the U.S. which contain a controlled substance are listed as Schedule II, III, IV or V, with Schedule II substances considered to present the highest potential for abuse or dependence and Schedule V substances the lowest relative risk of abuse among such substances. Schedule I and II drugs are subject to the strictest controls under the CSA, including manufacturing and procurement quotas, heightened security requirements and additional criteria for importation. In addition, dispensing of Schedule II drugs is further restricted. For example, they may not be refilled without a new prescription. Sunosi is a Schedule IV controlled substance.

Individual states have also established controlled substance laws and regulations. Though state-controlled substances laws often mirror federal law, they may separately schedule our products or our product candidates as well. We, or our partners, may also be required to obtain separate state registrations, permits or licenses in order to be able to manufacture, distribute, administer or prescribe controlled substances for clinical trials or commercial sale, and failure to meet applicable regulatory requirements could lead to enforcement and sanctions by the states in addition to those from the DEA or otherwise arising under federal law.

U.S facilities conducting research, manufacturing, distributing, importing or exporting, or dispensing controlled substances must be registered (licensed) to perform these activities and must comply with the security, control, recordkeeping and reporting obligations under the CSA, DEA regulations and corresponding state requirements. DEA and state regulatory bodies conduct periodic inspections of certain registered establishments that handle controlled substances. Obtaining and maintaining the necessary registrations and complying with the regulatory obligations may result in delay of the importation, manufacturing, distribution or clinical research of our products and product candidates. Furthermore, failure to maintain compliance with the CSA and DEA and state regulations by us or any of our contractors, distributors or pharmacies can result in regulatory action that could have a material adverse effect on our business, financial condition and results of operations. DEA and state regulatory bodies may seek civil penalties, refuse to renew necessary registrations, or initiate proceedings to restrict, suspend or revoke those registrations. In certain circumstances, violations could lead to criminal penalties. Any penalties imposed by the DEA to us or our third-party manufacturers could have a material adverse effect on our business, results of operations, financial condition and growth prospects.

RISKS RELATED TO OUR DEPENDENCE ON THIRD PARTIES

We rely, and expect to continue to rely, on third parties to perform many essential services for our products and product candidates, including services related to our preclinical studies and clinical trials, warehousing and inventory control, distribution, government price reporting, customer service, and adverse event reporting. If these third parties fail to perform satisfactorily, including by failing to meet deadlines for the completion of our preclinical studies and clinical trials, or fail to comply with legal and regulatory requirements, our ability to commercialize any of our products will be significantly impacted and we may be subject to regulatory sanctions.

We rely on third-parties to conduct, supervise, and monitor our preclinical studies and certain clinical trials for our product candidates and do not currently plan to independently conduct preclinical studies or clinical trials of any other potential product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions, and clinical investigators, to conduct our preclinical studies and clinical trials. While we have agreements governing their activities, we have limited influence over their actual performance and control only certain aspects of their activities. The failure of these third parties to successfully carry out their contractual duties or meet expected deadlines could substantially harm our business because we may not obtain marketing approval for or commercialize our product candidates in a timely manner, or at all. Moreover, these agreements 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 and adversely affect our business.

Our reliance on these third parties for development activities will reduce our control over these activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory, and scientific standards and our reliance on third parties does not relieve us of our regulatory responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our preclinical trials are conducted in accordance with GLP as appropriate. Moreover, the FDA and comparable foreign regulatory authorities require us to comply with standards, such as GCP for conducting, monitoring, 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. As a clinical trial sponsor, we also have regulatory requirements that directly apply to us. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators, and trial sites. If we or any of the third parties we engage fail to comply with applicable GCP, we, or those third parties, may be subject to enforcement or other legal actions, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials.

In addition, when we submit an NDA for review, we are required to report certain financial interests of our third-party investigators if these relationships exceed certain financial thresholds or meet other criteria. The FDA and comparable foreign regulatory authorities may question the integrity of the data from those clinical trials conducted by investigators who previously served or currently serve as scientific advisors or consultants to us from time to time and receive cash compensation in connection with such services or otherwise receive compensation from us that could be deemed to impact study outcome, proprietary interests in a product candidate, certain company equity interests, or significant payments of other sorts.

We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with GCP regulations. In addition, our clinical trials must be conducted with product candidates that were produced under 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 certain clinical trials and post the results of certain completed clinical trials on a government sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so or to meet the related submission requirements can result in enforcement actions, including civil monetary penalties and adverse publicity.

Third parties we engage to conduct research may also have relationships with other entities, some of which may be our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. In addition, these third parties are not our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our ongoing clinical, non-clinical, and preclinical programs. 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, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed, or terminated and we may 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, successfully commercialize our product candidates, or we or they may be subject to regulatory enforcement actions. As a result, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. To the extent we are unable to successfully identify and manage the performance of third-party service providers in the future, our business may be materially and adversely affected.

If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative resources or to do so on commercially reasonable terms. Switching or adding additional third parties involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new third party 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 these third-party vendors, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects, and results of operations.

If the manufacturers upon whom we rely fail to produce our products in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues.

We do not manufacture any of our products, and we do not currently plan to develop any capacity to do so. We currently outsource all manufacturing of our products to third parties typically without any guarantee that there will be sufficient supplies to fulfill our requirements or that we may obtain such supplies on acceptable terms. Any delays in obtaining adequate supplies with respect to our products may delay or disrupt the development or commercialization of our products. Moreover, we do not yet in all cases have agreements established regarding commercial supply of our product candidates, and we may not be able to establish or maintain commercial manufacturing arrangements on commercially reasonable terms for any of our current or future product candidates for which we obtain approval in the future.

We may not succeed in our efforts to establish manufacturing relationships or other alternative arrangements for any of our existing or future products and programs. Our products may compete with other products and product candidates for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that are both capable of manufacturing for us and willing to do so. If our existing third-party manufacturers, or the third parties that we engage in the future to manufacture a product for commercial sale or for our clinical trials, should cease to continue to do so for any reason, we likely would experience delays in obtaining sufficient quantities of our product for us to meet commercial demand or to advance our clinical trials while we identify and qualify replacement suppliers. If, for any reason we are unable to obtain adequate supplies of our products or the drug substances used to manufacture them, it will be more difficult for us to develop our products and compete effectively. Further, even if we do establish such collaborations or arrangements, our third-party manufacturers may breach, terminate, or not renew these agreements.

Any problems or delays we experience in preparing for commercial-scale manufacturing of a product candidate may result in a delay in FDA approval of the product candidate or may impair our ability to manufacture commercial quantities or such quantities at an acceptable cost, which could result in the delay, prevention, or impairment of clinical development and commercialization of our product candidates and could adversely affect our business. For example, our manufacturers will need to produce specific batches of our product candidates to demonstrate acceptable stability under various conditions and for commercially viable lengths of time. We and our contract manufacturers will need to demonstrate to the FDA and other regulatory authorities that this is acceptable stability data for our product candidates, as well as validate methods and manufacturing processes, in order to receive regulatory approval to commercialize any of our current or future product candidates. Furthermore, if our commercial manufacturers fail to deliver the required commercial quantities of bulk drug substance or finished product on a timely basis and at commercially reasonable prices, we would likely be unable to meet demand for our products and we would lose potential revenues.

We have a limited number of contract manufacturers for our products. At times, we may have only one manufacturer for a product. In addition, we do not have any long-term commitments from our suppliers of clinical trial material or guaranteed prices for our product candidates. The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production. These problems include difficulties with production costs and yields; quality control, including stability of the product candidate and quality assurance testing; shortages of qualified personnel; and compliance with strictly enforced federal, state, and foreign regulations. Our manufacturers may not perform as agreed. If our manufacturers were to encounter any of these difficulties, our ability to provide product candidates to patients in our clinical trials and for commercial use, if approved, would be jeopardized.

In addition, all manufacturers of our products must comply with cGMP requirements enforced by the FDA and comparable foreign regulatory authorities that are applicable to both finished drug products and active pharmaceutical ingredients used both for clinical and commercial supply, through its facilities inspection program. The FDA must verify our contract manufacturers' compliance with cGMP requirements and comparable foreign regulatory authorities will similarly inspect our contract manufacturers' facilities after we submit our marketing applications to the agency and comparable foreign regulatory authorities. The cGMP requirements include quality control, quality assurance, and the maintenance of records and documentation. Manufacturers of our products may be unable to comply with our specifications, these cGMP requirements and with other FDA, state, and foreign regulatory requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure or maintain regulatory approval for their manufacturing facilities. While we are ultimately responsible for the manufacture of our products, other than through our contractual arrangements, we have little control over our manufacturers' compliance with these regulations and standards. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our products or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop or market our products, or obtain regulatory approval for, our product candidates. A failure to comply with these requirements may result in regulatory enforcement actions against our manufacturers or us, including fines and civil and criminal penalties, including imprisonment; suspension or restrictions on production; suspension, delay, or denial of product approval or supplements to approved products; clinical holds or termination of clinical studies; warning or untitled letters; regulatory authority communications warning the public about safety issues with the drug; refusal to permit the import or export of the products; product seizure, detention, or recall; suits under the civil FCA; corporate integrity agreements; consent decrees; or withdrawal of product approval. If the safety of any quantities supplied is compromised due to our manufacturers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for our product candidates or successfully commercialize our products.

Any failure or refusal to supply our products or components for our current or future product candidates that we may develop could delay, prevent, or impair our clinical development or commercialization efforts. Any change in our manufacturers could be costly because the commercial terms of any new arrangement could be less favorable and because the expenses relating to the transfer of necessary technology and processes could be significant.

As an NDA applicant and commercial "virtual manufacturer," we may rely in many cases on third parties to perform many essential services for our products, including services related to warehousing and inventory control, distribution, government price reporting, customer service, and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize any of our products will be significantly impacted and we may be subject to regulatory sanctions.

We have retained third-party service providers to perform a variety of functions related to the sale and distribution of our products, key aspects of which are out of our direct control. These service providers provide key services related to warehousing and inventory control, distribution, government price reporting, and customer service, and, as a result, much of our inventory is stored at a single warehouse maintained by one such service provider. We substantially rely on this service provider as well as other third-party providers that perform services for us, including entrusting our inventories of products to their care and handling. If these third-party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired and we may be subject to regulatory enforcement action. Moreover, these agreements might terminate for a variety of reasons. If we fail to enter into alternative arrangements, this could further delay the commercialization of our products and adversely affect our business.

In addition, we may engage third parties to perform various other services for us relating to adverse event reporting, safety database management, fulfillment of requests for medical information regarding our products and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements related to adverse event reporting, we could be subject to regulatory sanctions.

Additionally, if a third party errs in calculating government pricing information from transactional data in our financial records, it could impact our discount and rebate liability and potentially cause government programs to overpay providers for our products, which could expose us to significant FCA liability and other civil monetary penalties.

Any collaboration arrangements that we are a party to or may enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize our product candidates.

Our business model is to commercialize our product candidates in the United States, and we may either commercialize products outside the United States ourselves or collaborate with pharmaceutical or biotechnology companies, or academic institutions, for the development or commercialization of our product candidates in the rest of the world. For example, we currently commercialize Sunosi in Canada. In February 2023, we announced a licensing transaction with Pharmanovia to market Sunosi in Europe and certain countries in the Middle East / North Africa. Our current and future collaboration arrangements may not be successful, and the success of them will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaboration arrangements. For clinical trials of our product candidates being conducted by our collaborators, for example, the Phase 2 clinical trial of AXS-05 for smoking cessation in collaboration with Duke University, we relied on timeline estimates provided by our collaborators for these trials. Such timeline estimates may differ materially from actual trial completion dates. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority.

We may license the right to market and sell our products under our collaborators' labeler codes. Alternatively, we may enter into agreements with collaborators to market and sell our products under our own labeler code, in which case errors and omissions by collaborators in capturing and transmitting transactional data may impact the accuracy of our government price reporting.

Collaborations with pharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation. Any future collaborations we might enter into may pose a number of risks, including:

- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any product candidates which achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could fail to make timely regulatory submissions for a product candidate;
- collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product candidate or product;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation, or the preferred course of development, might cause delays or termination of the research, development, or commercialization of product candidates, lead to additional responsibilities for us with respect to product candidates, or result in litigation or arbitration, any of which would be time consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation; and
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability.

If any collaborations we might enter into in the future do not result in the successful development and commercialization of products, or if one of our collaborators subsequently terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under the agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates and our product platform.

Additionally, if any future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our reputation in the business and financial communities could be adversely affected.

RISKS RELATED TO INTELLECTUAL PROPERTY

It is difficult and costly to protect our proprietary rights, and, as a result, we may not be able to ensure their protection. In addition, patents have a limited lifespan and will eventually expire.

Market exclusivity awarded by the FDA upon the approval of an NDA is limited in scope and duration. For example, our New Chemical Entity exclusivity for Sunosi expired on June 17, 2024 with an Orphan Drug Exclusivity relating to the product's narcolepsy indication expiring on June 17, 2026. For Auvelity, the New Product Exclusivity expires on August 18, 2025. Neither of these expiry dates take into account the effect of the statutory 30-month stay should we timely commence litigation against any generic filer. A generic filer may be permitted to launch a generic version of either of our products following expiry of these exclusivities if our patents do not preclude a generic launch. Patent litigation is inherently uncertain, and we cannot guarantee the outcome of any such proceedings or that we would succeed in stopping the "at risk" launch of a generic version of either of our currently commercialized products during the pendency of litigation following expiry of the 30-month stay. Such a generic launch could materially impact our commercial success.

We seek to protect intellectual property relating to our products and portfolio products by prosecuting patents in the United States and elsewhere. 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. Moreover, should we enter into additional collaborations we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance, and enforcement of our patent applications and patents. Therefore, these patents and patent applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. 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. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents and patent applications or in third-party patents and patent applications. The degree of future protection for our proprietary rights is uncertain because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. Moreover, the patent application process is also subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting any of our current or future product candidates that we may develop, license, or acquire by obtaining and defending patents. For example:

- we may not have been the first to conceive of and reduce to practice the inventions covered by each of our pending patent applications and issued patents;
- we may not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our product candidates or technologies;
- it is possible that none of the pending patent applications will result in issued patents;
- the issued patents may not cover commercially viable active products, may not provide us with any competitive advantages, or may be successfully challenged by third parties;
- we may not develop additional proprietary technologies that are patentable;
- patents of others may have an adverse effect on our business;

- noncompliance with requirements of governmental patent agencies can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction, potentially allowing competitors to enter the market earlier than would otherwise have been the case;

- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with, or eliminate our ability to make, use, and sell our potential product candidates; or

- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of available patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns.

Patents have a limited lifespan. In most countries, including the United States, the expiration of a patent is typically 20 years from the date that the application for the patent is filed or 20 years from the earliest non-provisional filing date to which priority is claimed if the patent is granted from a continuing application (e.g., continuation, divisional, or continuation-in-part). Various extensions of patent term may be available in particular countries; however, in all circumstances the life of a patent, and the protection it affords, has a limited term. If we encounter delays in obtaining regulatory approvals, the period of time during which we could market a product under patent protection could be reduced. We expect to seek extensions of patent terms where these are available in any countries where we are prosecuting patents. Such possible extensions include those permitted under the Drug Price Competition and Patent Term Restoration Act of 1984 in the United States, which permits a patent term extension of up to five years to cover an FDA-approved product. The actual length of the extension will depend on the amount of patent term lost while the product was in clinical trials. However, the applicable authorities, including the USPTO, and the FDA in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data, and then may be able to launch their product earlier than might otherwise be the case.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. In particular, under the Leahy-Smith Act, the United States transitioned in March 2013 to a “first to file” system in which the first inventor to file a patent application will be entitled to the patent. Third parties are allowed to submit prior art before the issuance of a patent by the USPTO and may become involved in post-grant proceedings including reexamination, post-grant review, inter-partes review, or derivation or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding, or litigation could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position. Future patent reform legislation in the U.S. and/or in jurisdictions outside the U.S. could potentially further increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents.

Obtaining and maintaining our patent protection depends on compliance with various procedural, documentary, fee payment, and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for noncompliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment, and other similar provisions during the patent prosecution process. Periodic maintenance fees, renewal fees, annuity fees, and various other governmental fees on patents or patent applications will be due to be paid to the USPTO and various patent agencies outside of the United States in several stages over the lifetime of the patents and applications. We have systems in place to remind us to pay these fees, and we employ and rely on reputable law firms and other professionals to effect payment of these fees to the USPTO and non-U.S. patent agencies for the patents and patent applications we own and those that we in-license. We also employ reputable law firms and other professionals to help us comply with the various documentary and other procedural requirements with respect to the patents and patent applications that we own and those that we in-license. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

If we, or any future collaboration partner, 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 sell any of our products depends upon our ability to avoid infringing the proprietary rights of third parties, and our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market, and sell our products and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the general field of treatment and management of CNS disorders and cover the use of numerous compounds and formulations in our targeted markets. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. 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 business, financial condition, results of operations, and prospects. Regardless of the outcome of any litigation, defending against 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 any of our current or future products may infringe. There could also be existing patents of which we are not aware that any of our current or future products may inadvertently infringe.

If a third-party claims that we infringe their intellectual property rights, we could face a number of issues, including:

- infringement and other intellectual property claims which, whether meritorious or not, 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 products and processes so they do not infringe, which may not be possible or could require substantial funds and time.

If we are found to infringe a third party's intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms, or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our products or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations, and prospects.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming, and unsuccessful.

Competitors may infringe our issued patents, our in-licensed patents, or other intellectual property that we own or in-license. Under the terms of our license agreements with Antecip, if we believe a third party is infringing on the patents subject to the licenses, we are obligated, at our own expense, to initiate suit against those third parties. 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 and/or to challenge the validity of the asserted patent(s) before a court or the USPTO (e.g., in post-grant proceedings such as Inter Partes Review before the Patent Trial and Appeal Board (PTAB) of the USPTO). In addition, in a patent infringement or validity proceeding, a decision maker (e.g., a court or the PTAB) 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 or related proceeding at the USPTO could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Many of our competitors are larger than we are and have substantially greater resources than we do. They are, therefore, likely to be able to sustain the costs of complex patent litigation longer than we could. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, in-license needed technology, or enter into development partnerships that would help us bring our product candidates to market.

We have licensed and may need to license certain intellectual property from third parties in the future. Such licenses may not be available or may not be available on commercially reasonable terms. Our business may be materially harmed if the licenses are not available or terminated for any reason.

We are a party to certain license agreements under which we are granted rights to intellectual property, including patent rights that are important to our business. We expect that we may need to enter into additional license agreements in the future to commercialize our products, in which case we would be required to obtain a license from additional third parties. Such licenses may not be available on commercially reasonable terms, or at all, which could materially harm our business, financial condition, results of operations, and prospects. We rely on these licenses to use intellectual property that may be material to our business and important or necessary to the development or commercialization of our products. Our existing license agreements impose, and we expect that future license agreements will impose on us, various exclusivity obligations. If we fail to comply with our obligations under these agreements, the applicable licensor may have the right to terminate our license, in which case we may not be able to develop or commercialize the products covered by such license.

In January 2020, we entered into an agreement with Pfizer for an exclusive U.S. license to Pfizer's clinical and nonclinical data, and intellectual property for reboxetine, the active pharmaceutical ingredient in AXS-12, which Axsome is developing for the treatment of narcolepsy. The agreement also provides Axsome exclusive rights to develop and commercialize esreboxetine, a new late-stage product candidate now referred to as AXS-14, in the U.S. for the treatment of fibromyalgia. Under the terms of the agreement, we received from Pfizer an exclusive U.S. license to Pfizer data for reboxetine and esreboxetine encompassing a full range of nonclinical studies, and short-term and long-term clinical trials involving more than five thousand patients. The licensed data includes results of a positive Phase 3 trial and a positive Phase 2 trial of esreboxetine in the treatment of fibromyalgia. We will have the exclusive right and sole responsibility of developing AXS-14 (esreboxetine) in the U.S. for the treatment of fibromyalgia and for other indications. Pfizer received 82,019 shares of our common stock having a value of $8.0 million, based on the average closing price of our common stock for the 10 prior trading days of $97.538, in consideration for the license and rights. Pfizer also received an upfront cash payment of $3.0 million and will receive up to $323 million in regulatory and sales milestones and tiered mid-single to low double-digit royalties on future sales. Pfizer will also have a right of first negotiation on any potential future strategic transactions involving AXS-12 and AXS-14. Under the agreement, we are obligated to use commercially reasonable efforts to develop, manufacture and commercialize the compounds and products in the United States and to seek and maintain regulatory approvals for the compounds and products. The agreement will expire on a product-by-product basis upon expiration of the last-to-expire royalty term for such product. On expiration (but not earlier termination), we will have a perpetual, non-exclusive, fully paid, royalty-free and irrevocable license under the licensed patent rights and related data to develop, manufacture, use, commercialize and otherwise exploit the compounds. Either party may terminate the agreement for the other party's material breach following a cure period. Pfizer may immediately terminate the agreement upon certain insolvency events relating to us. We may terminate the agreement for any reason upon ninety days written notice to Pfizer at any time after the first anniversary of the agreement. If the license agreement with Pfizer is terminated for any reason, our business, financial condition, results of operations, and prospects will be materially harmed.

In 2012, we entered into three exclusive license agreements with Antecip an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which we were granted exclusive licenses to develop, manufacture, and commercialize Antecip's patents and applications related to the development of AXS-05, as well as two product candidates that are not currently in development, anywhere in the world for human therapeutic, veterinary, and diagnostic use. The agreements were amended in August 2015 to update the schedule of patents and applications subject to the license agreements. Pursuant to the agreements, we are required to use commercially reasonable efforts to develop, obtain regulatory approval for, and commercialize AXS-05. Under the terms of the agreements, we are required to pay to Antecip a royalty equal to 3.0% for AXS-05, of net sales of products containing the licensed technology by us, our affiliates, or permitted sublicensees. These royalty payments are subject to reduction by an amount up to 50.0% of any required payments to third parties. Unless earlier terminated by a party for cause or by us for convenience, the agreements remain in effect on a product-by-product and country-by-country basis until the later to occur of (1) the applicable product is no longer covered by a valid claim in that country or (2) 10 years from the first commercial sale of the applicable product in that country. Upon expiration of the agreements with respect to a product in a country, our license grant for that product in that country will become a fully paid-up, royalty-free, perpetual non-exclusive license. If Antecip terminates any of the agreements for cause, or if we exercise our right to terminate any of the agreements for convenience, the rights granted to us under such terminated agreement will revert to Antecip. We are dependent upon the license agreements with Antecip and if any of the license agreements with Antecip are terminated for any reason, our business, financial condition, results of operations, and prospects will be materially harmed.

In connection with the Acquisition, in addition to the upfront purchase price, we assumed certain liabilities in connection with the Acquisition and agreed to make non-refundable, non-creditable royalty payments to Jazz on U.S. net sales. There are no royalty payments due to Jazz for net sales outside of the U.S. In addition, we assumed all of the commitments of Jazz to SK and Aerial. The assumed commitments to SK and Aerial include single-digit tiered royalties and certain sales and development milestones. We are dependent on these agreements, and if we breach these agreements, our business, financial condition, results of operations, and prospects will be materially harmed.

We may be subject to claims that our employees, independent contractors, or consultants have wrongfully used or disclosed alleged trade secrets of their former employers or other third parties.

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 individuals 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.

We may be unable to adequately prevent disclosure of trade secrets and other proprietary information.

We rely on trade secrets to protect our proprietary technological advances and know-how, especially where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. We rely in part on confidentiality agreements with our employees, consultants, contractors, outside scientific collaborators, sponsored researchers, and other advisors, including the third parties we rely on to manufacture our products, to protect our trade secrets and other proprietary information. However, any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets. Accordingly, these agreements may not effectively prevent disclosure of confidential information and may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. Costly and time-consuming litigation could be necessary to enforce and determine the scope of our proprietary rights. In addition, others may independently discover our trade secrets and proprietary information. Further, the FDA, as part of its Transparency Initiative, a proposal to increase disclosure and make data more accessible to the public, is currently considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future, if at all. Failure to obtain or maintain trade secret protection could enable competitors to use our proprietary information to develop products that compete with our products or cause additional, material adverse effects upon our competitive business position and financial results.

We, or our licensors, may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting, and defending patent applications and patents on products in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but where enforcement rights are not as strong as those in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our or our licensors' intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

RISKS RELATED TO LEGAL AND COMPLIANCE MATTERS

If we fail to comply with federal, state, and foreign healthcare laws, including laws governing fraud and abuse, transparency, health, and other data protection, information privacy and security, we could face substantial penalties and liabilities, and our business, financial condition, results of operations, and prospects could be adversely affected.

As a pharmaceutical company, we are subject to many federal and state healthcare laws, including those described in the "Business—Government Regulation and Product Approval" section of this Annual Report on Form 10-K, such as the federal Anti-Kickback Statute, the federal civil and criminal FCA, the civil monetary penalties statute, the Medicaid Drug Rebate Statute and other price reporting requirements, the Veterans Health Care Act of 1992, the Sunshine Act, HIPAA, the FCPA, the ACA, and other state and foreign laws. Even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid, or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse, disclosures, and patients' rights are and will be applicable to our business. We are subject to healthcare laws by both the federal government and the states in which we conduct our business as well as by other third parties, such as patients.

There are numerous other laws and legislative and regulatory initiatives at the federal and state levels addressing privacy and security concerns, and some state privacy and security laws apply in broader circumstances than HIPAA and its implementing regulations. For example, California enacted legislation – the CCPA, which went into effect in January 2020, as subsequently amended by the CPRA, passed on November 3, 2020. The CCPA, among other things, creates data privacy obligations for covered companies and provides new privacy rights to California residents, including the right to opt out of certain disclosures of their information. The CCPA also creates a private right of action with statutory damages for certain data breaches, thereby potentially increasing risks associated with a data breach. Further, many data privacy and security laws within the U.S. have concurrent jurisdiction, which could subject us to enforcement by multiple agencies under multiple statutes for the same conduct (e.g., FTC enforcement under Section 5, HHS-Office for Civil Rights enforcement under HIPAA, and actions by state Attorneys General for violation of applicable state laws). Since the passage of the CCPA, certain other states have passed similar laws that may also have similar impacts on our data processing practices and incurred costs. Some of these state laws have not taken effect, and we cannot predict if states will subsequently amend those laws, if other states will pass similar laws, or the costs and expenses that we will incur to comply with such laws.

In addition, EU member states and other foreign jurisdictions, including Switzerland, have adopted data protection laws and regulations which impose significant compliance obligations. Moreover, the collection and use of personal data, including health data, relating to individuals located in the EU, which was formerly governed by the provisions of the EU Data Protection Directive 95/46, was replaced with the EU GDPR in May 2018. The GDPR, which is wide-ranging in scope, imposes several requirements relating to the legal basis of the processing of personal data, the information provided to the individuals, the security and confidentiality of the personal data, data breach notification and the use of third-party processors in connection with the processing of personal data. The GDPR also imposes strict rules on the transfer of personal data out of the EEA to the U.S. and other non-EEA countries that do not provide a level of protection to personal data in line with the GDPR standard, provides an enforcement authority in each EU member state and imposes large penalties for noncompliance, including the potential for fines of up to €20 million or 4% of the annual global turnover of the noncompliant company, whichever is greater. The GDPR requirements apply not only to third-party transactions, but also to transfers of information between us and our subsidiaries, including employee information. The recent coming into force of the GDPR has increased our responsibility and liability in relation to personal data that we process, including in clinical trials, and we may in the future be required to put in place additional mechanisms to ensure compliance with the GDPR, which could divert management's attention and increase our cost of doing business. Moreover, new regulation or legislative actions regarding data privacy and security (together with applicable industry standards) may increase our costs of doing business. In this regard, we expect that there will continue to be new proposed laws, regulations and industry standards relating to privacy and data protection in the United States, the EU and other jurisdictions, and we cannot determine the impact such future laws, regulations and standards may have on our business.

If we, or our operations, are found to be in violation of any federal or state healthcare, data or information privacy law, or any other governmental regulations that apply to us, we may be subject to penalties, including civil, criminal, and administrative penalties, damages, fines, disgorgement, debarment from government contracts, refusal of orders under existing contracts, exclusion from participation in U.S. federal or state health care programs, corporate integrity agreements, and the curtailment or restructuring of our operations, any of which could materially adversely affect our ability to operate our business and our financial results. 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 but not limited to, exclusions from participation in government healthcare programs, which could also materially affect our business.

Although an effective compliance program can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Moreover, achieving and sustaining compliance with applicable federal and state fraud laws may prove costly. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business.

If the government or third-party payors fail to provide adequate coverage and payment rates for any of our products, or if such payors and health care providers including health maintenance organizations (HMOs) and long-term care facilities choose to use therapies that are less expensive, our revenue and prospects for profitability may be limited.

In both domestic and foreign markets, sales of our products 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 organizations, private health insurers, and other similar programs and organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Many private payors employ "new-to-market blocks" for newly launched medications and other products until the payors have had the opportunity to make a coverage decision based upon their internal review of such products. When a medication or other product is not covered, the patient or other third party is responsible to pay the full price, which can significantly limit utilization. If reimbursement is not available, or is available only up to limited levels, our product candidates may be competitively disadvantaged, and we, or our collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or our collaborators, to establish or maintain a market share sufficient to realize a sufficient return on our or their investments. Alternatively, securing favorable reimbursement terms may require us to compromise pricing and prevent us from realizing an adequate margin over cost.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing, and reimbursement for new drug products varies widely from country to country. Current and future legislation and/or administrative action may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. For example, on September 20, 2024, the Centers for Medicare & Medicaid Services issued a final rule titled "Medicaid Program; Misclassification of Drugs, Program Integrity Updates Under the Medicaid Drug Rebate Program," which may impact our reimbursement and rebate strategy. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenues we are able to generate from the sale of the product in that country. Additionally, drug pricing is a key state and federal issue within the U.S., with recent legislation and additional proposals designed to bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare and Medicaid, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. We expect continued focus and pressure on drug pricing going forward. Adverse pricing limitations may hinder our ability or the ability of our collaborators to recoup our or their investment in one or more of our products or product candidates. Our ability, and the ability of our collaborators, to commercialize our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from government healthcare programs, private health insurers, and other organizations. Regulatory authorities and third-party payors, such as private health insurers and HMOs, decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Several third-party payors are requiring that drug companies provide them with predetermined discounts from list prices, are using preferred drug lists to leverage greater discounts in competitive classes, are disregarding therapeutic differentiators within classes, and are challenging the prices charged for drugs. Brand drugs without generic equivalents are often included in therapeutic classes with other brands that have generic versions and may be similarly disadvantaged by the availability of low-cost alternatives within the class, particularly if a generic version of the same agent is available in another form.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. Third-party coverage and reimbursement for our products or product candidates for which we receive regulatory approval may not be available or adequate in either the United States or international markets, which could have a negative effect on our business, financial condition, results of operations, and prospects.

Assuming coverage is approved, the resulting reimbursement payment rates might not be adequate. If payors subject our products to maximum payment amounts or impose limitations that make it difficult to obtain reimbursement, providers may choose to use therapies which are less expensive or have fewer access restrictions when compared to our product candidates. Additionally, if payors require high copayments, beneficiaries may decline prescriptions and seek alternative therapies. We may need to conduct post-marketing studies in order to demonstrate the cost effectiveness of any of our products to the satisfaction of hospitals and 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. Our products 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.

In addition, federal programs impose penalties on manufacturers of drugs marketed under an NDA, including 505(b)(2) drugs, in the form of mandatory additional rebates and/or discounts if commercial prices increase at a rate greater than the Consumer Price Index Urban, and these rebates and/or discounts, which can be substantial, may impact our ability to raise commercial prices. Regulatory authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of our collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost effective, and coverage and reimbursement may not be available to our customers, or those of our collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost control initiatives could cause us, or our collaborators, to decrease, discount, or rebate a portion of the price we, or they, might establish for products, which could result in lower than anticipated product revenues. If the realized prices for our products, if any, decrease or if governmental and other third-party payors do not provide adequate coverage or reimbursement, our prospects for revenue and profitability will suffer.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale, and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may only be temporary. Reimbursement rates may vary, by way of example, according to the use of the drug and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

Prices paid for a drug also vary depending on the class of trade. Prices charged to government customers are subject to price controls, including ceilings, and private institutions obtain discounts through group purchasing organizations. Net prices for drugs may be further reduced by mandatory discounts or rebates required by government healthcare programs and demanded by private payors. Drugs approved under NDAs, including 505(b)(2) drugs, are subject to greater discounts and reporting obligations under federal programs than drugs approved under ANDAs, and the inflation penalty applicable to these products can equal the selling price. It is also not uncommon for market conditions to warrant multiple discounts to different customers on the same unit, such as purchase discounts to institutional care providers and rebates to the health plans that pay them, which reduces the net realization on the original sale.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We, and our collaborators, cannot be sure that coverage will be available for any product that we, or they, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government funded and private payors for any of our product candidates for which we obtain marketing approval could have a material adverse effect on our operating results, ability to raise capital needed to commercialize products, and overall financial condition.

We are subject to new legislation, regulatory proposals, and healthcare payor 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 some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities, and affect our ability, or the ability of our collaborators, to profitably sell any products for which we obtain marketing approval. It is unclear what impact these various efforts have and will have on our business operations and resulting financial condition. We expect that current laws, as well as 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, or our collaborators, may receive for any approved products.

We are unable to predict the future course of federal or state healthcare legislation in the United States directed at broadening the availability of healthcare and containing or lowering the cost of healthcare, including drugs and biologics. Any further changes in the law or regulatory framework that reduce our revenue or increase our costs could also have a material and adverse effect on our business, financial condition and results of operations.

We expect that federal and state healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria, increased regulatory burdens and operating costs, decreased net revenue from our pharmaceutical products, decreased potential returns from our development efforts, and additional downward pressure on the price that we receive for any approved drug. There is also an increasing focus on the price of drugs, both at the state and federal levels, and it is likely that additional pricing controls will be enacted and could harm our business, financial condition and results of operations. For instance, states such as California have begun enacting transparency laws aimed at curbing drug price increases. We continue to monitor the potential impact of proposals and recently enacted legislation to lower prescription drug costs at the federal and state level. For example, the IRA was signed into law by President Biden in August 2022. The IRA makes significant changes to how drugs are covered and paid for under the Medicare program, including the creation of financial penalties for drugs whose prices rise faster than the rate of inflation, redesign of the Medicare Part D program to require manufacturers to bear more of the liability for certain drug benefits, and government price-setting for certain Medicare Part D drugs, starting in 2026, and Medicare Part B drugs starting in 2028. The IRA's changes include, by way of example, capping Medicare beneficiary out-of-pocket spending at $2,000 for 2025 and providing for no beneficiary cost sharing above the annual out-of-pocket threshold. Additionally, as of January 1, 2025, the existing Medicare Coverage Gap Discount Program ended and was replaced by the Manufacturer Discount Program, through which a manufacturer provides discounts for brand-name drugs and biologics in the initial and catastrophic coverage phases under the Medicare Part D benefit. These changes eliminated the Medicare Part D coverage gap benefit phase (commonly referred to as the "donut hole"), in which a Medicare beneficiary was originally responsible for 100% of the costs of covered prescription drugs following an initial coverage phase until the costs initiated a catastrophic coverage phase, but which was gradually phased out through the end of 2024. We are evaluating what effect, if any, the IRA may have on our business. 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 drugs.

Legislative and regulatory proposals may also be 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 our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress 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.

In addition, there have been a number of other legislative and regulatory proposals aimed at changing the pharmaceutical industry. For instance, the enacted DSCSA imposes obligations on manufacturers of prescription drug products for commercial distribution, regulating the distribution of the products at the federal level, and sets certain standards for federal or state registration and compliance of entities in the supply chain (manufacturers and repackagers, wholesale distributors, third-party logistics providers, and dispensers). The DSCSA preempts certain previously enacted state pedigree laws and the pedigree requirements of the PDMA. Trading partners within the drug supply chain must now ensure certain product tracing requirements are met; that they are doing business with other authorized trading partners; and they are required to exchange transaction information, transaction history, and transaction statements. Product identifier information (an aspect of the product tracing scheme) is also now required. The DSCSA requirements, development of standards, and the system for product tracing have been and will continue to be phased in over a period of years. The distribution of product samples continues to be regulated under the PDMA, and some states also impose regulations on drug sample distribution.

Compliance with the federal track and trace requirements may increase our operational expenses and impose significant administrative burdens. As a result of these and other new proposals, we may determine to change our current manner of operation, provide additional benefits, or change our contract arrangements, any of which could have a material adverse effect on our business, financial condition, and results of operations.

In the EU, recently adopted and pending legislation will impact regulatory procedures for medicinal products. Key developments include Regulation (EU) 2021/2282 on health technology assessment (HTA Regulation), which became applicable in the EU on 12 January 2025. Additionally, in April 2023, the EC adopted a proposal to revise the EU pharmaceutical legislation consisting of a new directive and a new regulation that would replace Directive 2001/83/EC and Regulation (EC) 726/2004, among others. In April 2024, the European Parliament introduced amendments to the EC's proposal. The EU legislative process remains ongoing, with several stages still required before the reform can receive final approval. If approved, the reform would mark the most significant overhaul of EU pharmaceutical law since 2004, with a wide range of impacts including on approval procedures, regulatory data protection, or RDP, and the so-called "Bolar exemption," among others.

We are subject to a variety of U.S. and international laws and regulations.

We are currently subject to a number of government laws and regulations, and, in the future, could become subject to new government laws and regulations. The costs of compliance with such laws and regulations, or the negative results of non-compliance, could adversely affect our business, cash flow, results of operations, financial condition, and prospects; these laws and regulations include (i) additional health care reform initiatives in the U.S. or in other countries, including additional mandatory discounts or fees; (ii) the FCPA or other anti-bribery and corruption laws; (iii) new laws, regulations, and judicial or other governmental decisions affecting pricing, drug reimbursement, and access or marketing within or across jurisdictions; (iv) changes in intellectual property laws; (v) changes in accounting standards; (vi) new and increasing data privacy regulations and enforcement, particularly in the EU, the U.S., and China; (vii) legislative mandates or preferences for local manufacturing of pharmaceutical products; (viii) emerging and new global regulatory requirements for reporting payments and other value transfers to healthcare professionals; (ix) environmental regulations, such as the EU's Corporate Sustainability Reporting Directive; and (x) the potential impact of importation restrictions, embargoes, trade sanctions, and legislative and/or other regulatory changes.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In international markets, reimbursement and health care payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be available, or that the third-party payors' reimbursement policies will not adversely affect our ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Our employees, independent contractors, consultants, commercial partners, principal investigators, or CROs may engage in misconduct or other improper activities, including noncompliance with 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, independent contractors, consultants, commercial partners, principal investigators, or CROs could include intentional, reckless, negligent, or unintentional failures to comply with FDA regulations, comply with applicable fraud and abuse laws, provide accurate information to the FDA, report financial information or data accurately, or disclose unauthorized activities to us. This misconduct could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter this type of misconduct, and 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, financial condition, and results of operations, including the imposition of significant fines or other sanctions. Further, even if we are successful in mounting a defense, we may incur substantial costs in preparing and maintaining our defense and any such action would be time- and resource-intensive and potentially divert management's attention from the business, which could adversely affect our ability to operate our business and our results of operations.

Our third-party manufacturers may use hazardous materials in the production of our products and, if so, they must comply with environmental laws and regulations, which can be expensive and restrict how we or they do business.

Manufacturing activities for the production of our products involve the controlled storage, use, and disposal of hazardous materials, including the components of our products, and other hazardous compounds. Our third-party manufacturers and we are subject to federal, state, and local laws and regulations governing the use, manufacture, storage, handling, release, and disposal of, and exposure to, these hazardous materials. Violation of these laws and regulations could lead to substantial fines and penalties. Although we believe that our safety procedures, and those of our third-party manufacturers, 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 an accident, state or federal authorities may curtail our use of these materials and interrupt our business operations. In addition, we could become subject to potentially material liabilities relating to the investigation and cleanup of any contamination, whether currently unknown or caused by future releases.

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.

RISKS RELATED TO OUR BUSINESS OPERATIONS

We have and may continue to significantly increase the size of our organization, and we may experience difficulties in managing growth. If we are unable to implement appropriate controls and procedures to manage our growth, we will not be able to implement our business plan successfully.

As of February 11, 2025, we had 683 full-time employees. Our management, personnel, systems, and facilities currently in place may not be adequate to support future growth. In addition, we may not be able to recruit and retain qualified personnel in the future, particularly for sales and marketing positions, due to competition for personnel among pharmaceutical businesses, and the failure to do so could have a significant negative impact on our future product revenues and business results. Further, the value to employees of stock options or restricted stock units that vest over time is significantly affected by movements in our stock price that are beyond our control and may at any time be insufficient to counteract more lucrative offers from other companies. Our need to effectively manage our operations, growth and various projects requires that we:

- continue the hiring and training of personnel for our commercial organization, and maintain appropriate systems, policies and infrastructure to support that organization;
- ensure that our consultants and other service providers successfully carry out their contractual obligations, provide high quality results, and meet expected deadlines;
- continue to carry out our own contractual obligations to our licensors and other third parties; and
- continue to improve our operational, financial, and management controls, reporting systems, and procedures.

We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our development and commercialization goals.

Our continued growth could strain our personnel resources and infrastructure, and if we are unable to implement appropriate controls and procedures to manage our growth, we will not be able to implement our business plan successfully.

As we continue to complete our clinical trials and commercialize our product candidates, and as our company continues to grow, we may experience significant strains on our resources, including to our administrative, operational and financial infrastructure, which will result in additional burdens on management. Our success will depend in part upon the ability of our senior management to manage this growth effectively. To do so, we must continue to hire, train and manage new employees as needed. If our new hires perform poorly, or if we are unsuccessful in hiring, training, managing and integrating these new employees, or if we are not successful in retaining our existing employees, our business would be harmed. To manage the expected growth of our operations and personnel, we will need to continue to improve our operational, financial and management controls and our reporting systems and procedures.

We may acquire businesses or products, or form strategic alliances in the future, and we may not realize the benefits of such acquisitions or alliances.

We may acquire additional businesses or products, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to successfully integrate them with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing, and marketing any new products resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that, following any such acquisition, we will achieve the expected synergies to justify the transaction.

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

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the skills and leadership of our management team, including Dr. Herriot Tabuteau, our Chief Executive Officer and Chairman of the Board. We do not have formal employment agreements with any of our management team. However, we typically enter into offer letters with our executive officers and key personnel. Our senior management may terminate their employment with us at any time. If we lose one or more members of our senior management team, our ability to successfully implement our business strategy could be seriously harmed. Replacing these employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of, and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain, or motivate additional key personnel. We do not maintain "key person" insurance for any of our executives or other employees.

If we fail to maintain an effective system of internal controls over financial reporting, we may not be able to accurately report our financial condition, results of operations or cash flows, which may adversely affect investor confidence in us and, as a result, the value of our common stock.

As a public company, we continue to incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act, as well as rules subsequently implemented by the SEC and The Nasdaq Stock Market LLC, or Nasdaq, impose various requirements on public companies, including requiring establishment and maintenance of effective disclosure controls and internal control over financial reporting and changes in corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and have made some activities more time-consuming and costly.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure controls and procedures. Under Section 404(a) of the Sarbanes-Oxley Act, we are required to furnish a report by management on, among other things, the effectiveness of our internal control over financial reporting. This report must include disclosure of any material weaknesses identified by our management during its periodic assessment of our internal control over financial reporting. A material weakness is a deficiency, or combination of deficiencies, in internal control over financial reporting that results in more than a reasonable possibility that a material misstatement of annual or interim financial statements will not be prevented or detected on a timely basis. Section 404(b) of the Sarbanes-Oxley Act also requires our independent auditors to attest to, and report on, this management assessment. Ensuring that we have adequate internal controls in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort. If we are not able to comply with the requirements of Section 404, or if we, or our independent registered public accounting firm, are unable to attest to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our stock could decline and we could be subject to sanctions or investigations by Nasdaq, the SEC, or other regulatory authorities, which would require additional financial and management resources.

During the evaluation and testing process, if we identify one or more material weaknesses in our internal control over financial reporting, we would be required to implement remediation procedures aimed at mitigating the control weakness or weaknesses. Until such remediation procedures succeed in mitigating the control weakness or weaknesses, we would be unable to assert that our internal control over financial reporting is effective. We cannot assure you that there will not be material weaknesses in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to timely and accurately report our financial condition, results of operations or cash flows. The cost of compliance with Section 404 requires us to incur substantial accounting expense and expend significant management time on compliance-related issues as we implement additional corporate governance practices and comply with reporting requirements. Although we currently use the services of a third-party accounting firm to assist us with internal controls, we currently do not have an internal audit group, and we may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge.

Moreover, if we are not able to comply with these requirements in a timely manner, or if we, or our independent registered public accounting firm, identifies deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, the market price of our stock could decline, we could lose investor confidence in the accuracy and completeness of our financial reports, and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities, which would require additional financial and management resources. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

In addition, as discussed above, the Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting. In particular, Section 404 of the Sarbanes-Oxley Act requires us to perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on, and our independent registered public accounting firm to attest to, the effectiveness of our internal control over financial reporting. Pursuant to Section 404, we are required to provide an annual management report on the effectiveness of our internal control over financial reporting and we will also be required to include with such annual report an attestation report on internal controls over financial reporting issued by our independent registered public accounting firm. In the future, our independent registered public accounting firm may issue a report that is adverse in the event that we have not maintained effective internal controls over financial reporting, in all material respects. Any failure to maintain effective disclosure controls and internal control over financial reporting could have a material and adverse effect on our business, results of operations and financial condition and could cause a decline in the trading price of our common stock.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

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

Despite our implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war, telecommunication and electrical failures, cyber-attacks or cyber-intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. If such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our product candidate development programs. For example, the loss of clinical trial data from completed, ongoing, or planned clinical trials 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 were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential, or proprietary information, we could incur liability and the further development of any of our product candidates could be delayed.

Environmental, social, and governance matters may impact our business and reputation.

Governmental authorities, non-governmental organizations, customers, investors, external stakeholders and employees are increasingly sensitive to environmental, social, and governance, or ESG concerns, such as diversity and inclusion, climate change, water use, recyclability or recoverability of packaging, and plastic waste. This focus on ESG concerns may lead to new requirements that could result in increased costs associated with developing, manufacturing and distributing our products. Our ability to compete could also be affected by changing customer preferences and requirements, such as growing demand for more environmentally friendly products, packaging or supplier practices, or by failure to meet such customer expectations or demand. While we strive to improve our ESG performance, we risk negative stockholder reaction, including from proxy advisory services, as well as damage to our brand and reputation, if we do not act responsibly, or if we are perceived to not be acting responsibly in key ESG areas, including equitable access to medicines and vaccines, product quality and safety, diversity and inclusion, environmental stewardship, support for local communities, corporate governance and transparency, and addressing human capital factors in our operations. If we do not meet the ESG expectations of our investors, customers and other stakeholders, we could experience reduced demand for our products, loss of customers, and other negative impacts on our business and results of operations.

In addition, this emphasis on environmental, social, and other sustainability matters has resulted and may result in the adoption of new laws and regulations, including new reporting requirements. If we fail to comply with new laws, regulations, or reporting requirements, our reputation and business could be adversely impacted.

RISKS RELATED TO OWNERSHIP OF OUR COMMON STOCK

An active trading market for our common stock may not be sustained.

In November 2015, we closed our initial public offering. Prior to our initial public offering, there was no public market for shares of our common stock. Although we have completed our initial public offering and shares of our common stock are listed and trading on The Nasdaq Global Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or sell their shares at or above the prices at which they acquired their shares or sell their shares at the time they would like to sell. Any inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares.

The market price of our common stock may be highly volatile.

The trading price of our common stock is likely to be highly volatile. For example, in 2019, we experienced an extraordinary level of appreciation in our stock price. Such levels of gain are unlikely to continue in the future. Since then, we have seen both significant appreciations and depreciations in our stock price. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- the commercial success of our products;
- delays in the commencement, enrollment, and ultimate completion, of our planned and ongoing Phase 3 clinical trials for our product candidates;
- any delay or refusal on the part of the FDA in approving an NDA for any of our current and future product candidates;
- operating and stock price performance of other companies that investors deem comparable to ours;
- recommendations by securities analysts;
- news relating to our industry as a whole and news relating to trends in our markets;

- results of clinical trials of any of our current and future product candidates or those of our competitors;
- actual or anticipated variations in quarterly or annual operating results;
- failure to meet or exceed financial projections we provide to the public, if any;
- failure to meet or exceed the estimates and projections of the investment community, including securities analysts;
- introduction of competitive products or technologies;
- changes or developments in laws or regulations applicable to our product candidates;
- the perception of the pharmaceutical industry by the public, legislatures, regulators, and the investment community;
- general economic and market conditions and overall fluctuations in U.S. equity markets;
- data or security breaches;
- developments concerning our sources of manufacturing supply, warehousing, and inventory control;
- disputes or other developments relating to patents or other proprietary rights;
- additions or departures of key scientific or management personnel;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- capital commitments;
- investors' general perception of our company and our business;
- announcements and expectations of additional financing efforts, including the issuance of debt, equity or convertible securities;
- sales of our common stock, including sales by our directors and officers or significant stockholders;
- changes in the market valuations of companies similar to us;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, or divestitures;
- general conditions or trends in our industry; and
- the other factors described in this "Risk Factors" section.

In addition, the stock market in general, and the market for mid-cap pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance.

If equity research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business, or our market, our stock price and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that equity research analysts publish about us and our business. We do not have any control over the equity research analysts that provide research coverage of our common stock or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrades our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- the commercial success of our products;
- whether the FDA requires us to complete additional, unanticipated studies, tests, or other activities prior to approving any of our current and future product candidates, which may delay any such approval;
- our ability to identify and enter into third-party manufacturing arrangements capable of manufacturing any of our current or future product candidates in commercial quantities;
- our execution of other collaborative, licensing, or similar arrangements and the timing of payments we may make or receive under these arrangements;
- variations in the level of expenses related to our future development programs;
- any product liability or intellectual property infringement lawsuit in which we may become involved;
- regulatory developments affecting our current products, or the products of our competitors; and
- the level of underlying demand for our products.

If our quarterly or annual operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly or annual fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

Raising additional funds by issuing securities may cause dilution to existing stockholders and raising funds through lending and licensing arrangements may restrict our operations or require us to relinquish proprietary rights.

We may finance our cash needs through a combination of equity offerings, debt financings, grants, and license and development agreements in connection with any collaborations until such time, if ever, as our product sales are sufficient to meet our cash needs. To the extent that we raise additional capital by issuing equity securities, our existing stockholders' ownership will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common 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. Any debt financing we enter into may involve covenants that restrict our operations. These restrictive covenants may include limitations on additional borrowing and specific restrictions on the use of our assets as well as prohibitions on our ability to create liens, pay dividends, redeem our stock, or make investments. 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 product candidates that we would otherwise prefer to develop and market ourselves.

Our principal stockholders and management own a significant percentage of our stock and may be able to exert significant control over matters subject to stockholder approval.

As of February 11, 2025, our executive officers, directors, and 5% stockholders and their affiliates beneficially owned an aggregate of approximately 44% of our outstanding common stock. As a result, these stockholders have significant influence and may be able to determine all matters requiring stockholder approval. For example, these stockholders may be able to control elections of directors, amendments of our organizational documents, or approval of any merger, sale of assets, or other major corporate transaction. This concentration of ownership could delay or prevent any acquisition of our company on terms that other stockholders may desire and may adversely affect the market price of our common stock.

Some of these persons or entities may have interests different than our other stockholders. For example, these stockholders, if they acted together, could significantly influence all matters requiring approval by our stockholders, including the election of directors and the approval of mergers or other business combination transactions. These stockholders may be able to determine all matters requiring stockholder approval. The interests of these stockholders may not always coincide with our interests or the interests of other stockholders. This may also prevent or discourage unsolicited acquisition proposals or offers for our common stock that other stockholders may feel are in their best interest and our large stockholders may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock.

Sales of a substantial number of shares of our common stock in the public market by our existing stockholders could cause our stock price to fall.

Sales of a substantial number of shares of our common stock in the public market or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise adequate capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

As of February 11, 2025, we have outstanding 48,765,403 shares of common stock and 9,570,909 shares of common stock equivalents that would increase the number of common stock outstanding if these instruments were exercised or converted, including stock options to purchase common stock based on vesting requirements and warrants to purchase common stock, as well as outstanding restricted stock units. Of our currently outstanding shares of common stock, 40,726,651 are freely tradable. The remainder of the outstanding shares of common stock are held by our affiliates and may be considered “control securities” for purposes of Rule 144 under the Securities Act.

In addition, we have filed, or will soon file, one or more registration statements on Form S-8 registering the issuance of an aggregate of 15,600,010 shares of common stock subject to options or other equity awards issued or reserved for issuance under our 2015 Omnibus Incentive Compensation Plan and 1,100,000 shares of common stock reserved for issuance under our 2023 Employee Stock Purchase Plan. Shares registered under registration statements on Form S-8 will be available for sale in the public market subject to vesting arrangements and exercise of options, the lock up agreements described above and the restrictions of Rule 144 in the case of our affiliates.

Our management will have broad discretion in the use of the net proceeds from our capital raises, including the proceeds from sales pursuant to our Sales Agreement, and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from our capital raises, which we refer to as our Capital Raises, including the proceeds from sales pursuant to the March 2022 Sales Agreement with Leerink, which provides for the sale of up to $250.0 million of our common stock from time to time, and our stockholders will not have the opportunity as part of their investment decision to assess whether the net proceeds from our Capital Raises are being used appropriately. Our stockholders may not agree with our decisions, and our use of the proceeds may not yield any return on investment for our stockholders. Because of the number and variability of factors that will determine our use of the net proceeds from our Capital Raises their ultimate use may vary substantially from their currently intended use. Our failure to apply the net proceeds of our Capital Raises effectively could compromise our ability to pursue our growth strategy and we might not be able to yield a significant return, if any, on our investment of those net proceeds. Our stockholders will not have the opportunity to influence our decisions on how to use our net proceeds from our Capital Raises. Pending their use, we may invest the net proceeds from our Capital Raises in short-term, investment-grade, interest-bearing instruments and U.S. government securities. These temporary investments are not likely to yield a significant return.

The use of our net operating loss carryforwards and research tax credits may be limited.

Our net operating loss carryforwards and any future research and development tax credits may expire and not be used. As of December 31, 2024, we had U.S. federal net operating loss, or NOL, carryforwards of approximately $572.1 million and foreign NOL carryforwards of $4.8 million. U.S. federal net operating loss carry forwards amounting to $59.8 million generated before the 2018 tax year will start expiring beginning 2032, if we have not used them prior to that time, and the U.S. federal net operating losses of approximately $512.3 million generated in 2018 and later have an indefinite carryforward period. Net operating loss carry forwards arising in taxable years ending after December 31, 2017, are no longer subject to expiration under the Internal Revenue Code of 1986, as amended, or the Code. Additionally, our ability to use any net operating loss and credit carryforwards to offset taxable income or tax, respectively, in the future will be limited under Sections 382 and 383 of the Code, respectively, if we have a cumulative change in ownership of more than 50% within a three-year period. In the event a change of ownership occurs, we will be limited regarding the amount of net operating loss carryforwards and research tax credits that could be utilized annually in the future to offset taxable income or tax, respectively. Any such annual limitation may significantly reduce the utilization of the net operating loss carryforwards and research tax credits before they expire. In addition, certain states have suspended use of net operating loss carryforwards for certain taxable years, and other states are considering similar measures. As a result, we may incur higher state income tax expense in the future. Depending on our future tax position, continued suspension of our ability to use net operating loss carryforwards in states in which we are subject to income tax could have an adverse impact on our results of operations and financial condition.

Because we do not intend to pay dividends on our common stock, returns for our stockholders will be limited to any increase in the value of our stock.

We have never declared or paid any cash dividends on our capital stock. In addition, the terms of our existing credit facility with Hercules preclude us from paying cash dividends without Hercules' consent. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business and do not anticipate declaring or paying any cash dividends on our common stock for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock, if any. Investors seeking cash dividends should not purchase our common stock.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result.

There are provisions in our amended and restated certificate of incorporation and amended and restated bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our Board will have the authority to issue up to 10,000,000 shares of preferred stock and to fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. We do not currently have any preferred stock outstanding. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders.

In addition, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, or DGCL, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business combinations with particular stockholders of those companies. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Our amended and restated certificate of incorporation designates the Court of Chancery of the State of Delaware as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternate forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, employees or agents to us or our stockholders, (3) any action asserting a claim arising pursuant to the DGCL, or (4) any other action asserting a claim against us that is governed by the internal affairs doctrine, in each such case subject to such Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein.

Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our amended and restated certificate of incorporation described above. This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees or agents, which may discourage such lawsuits against us and our directors, officers, employees, and agents. Further, this choice of forum provision does not preclude or contract the scope of exclusive federal or concurrent jurisdiction for any actions brought under the Securities Act or the Exchange Act. Section 27 of the Exchange Act creates exclusive federal jurisdiction over all suits brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. As a result, the exclusive forum provision will not apply to suits brought to enforce any duty or liability created by the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction. In addition, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all suits brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder. As a result, the exclusive forum provision will not apply to suits brought to enforce any duty or liability created by the Securities Act or any other claim for which the federal and state courts have concurrent jurisdiction. Accordingly, our exclusive forum provision will not relieve us of our duties to comply with the federal securities laws and the rules and regulations thereunder, and our stockholders will not be deemed to have waived our compliance with these laws, rules and regulations.

If a court were to find these provisions of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs associated with resolving such matters in other jurisdictions, which could adversely affect our business, financial condition, and results of operations. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management and other employees.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 1C. CYBERSECURITY

Cybersecurity Governance and Responsibilities

The Board recognizes that cybersecurity represents an important component of the Company's overall enterprise risk management, or ERM. The Company seeks to mitigate cybersecurity risks through a cross-functional approach, including its Cybersecurity Committee, focused on preserving the confidentiality, security, and availability of the information that the Company collects and stores by assessing, identifying, preventing, and managing risks from cybersecurity threats and effectively responding to cybersecurity incidents when they occur.

Our Head of Information Technology (IT) oversees overall cybersecurity management, including appropriate risk mitigation strategies, systems, processes, and controls and provides periodic, but at least annually, reports to our Board or the Audit Committee of the Board of Directors, or the Audit Committee. The IT security team has over 40 years of combined technology experience, and over 20 years of experience in safeguarding and monitoring networks and systems, responding to incidents, and reducing the risk of business exposure. The Company's Cybersecurity Committee is comprised of information technology, finance, legal, human resources, and data privacy employees, including the Head of IT. It meets regularly, but at least annually, to review and provide oversight of the Company's cybersecurity risks and data security programs, policies, and strategies. Pursuant to internal policies, the Head of IT will notify the Cybersecurity Committee of significant cybersecurity incidents and breaches. The Cybersecurity Committee reviews, analyzes, and responds to cybersecurity incidents and breaches. Additional responsibilities and risk mitigation strategies relate to business continuity and business resiliency capabilities.

The Company's Audit Committee has the responsibility to review and discuss with management the Company's guidelines, policies, and governance with respect to financial risk exposures and ERM, including with respect to cybersecurity, and to report to the Board annually. The Audit Committee is also responsible for overseeing the integrity and effectiveness of the Company's disclosure controls and procedures, which are designed to ensure that information related to cybersecurity risks and incidents is recorded, processed, summarized, and reported accurately and on a timely basis, to allow for timely decisions regarding disclosure of any such incidents. Our Audit Committee receives regular presentations and reports on cybersecurity risks from the executive management leadership team, which address recent developments, evolving standards, vulnerability assessments, third-party and independent reviews, the threat environment, technological trends, and information security considerations arising with respect to the Company's peers and third parties. The Audit Committee is also made aware of any potential material cybersecurity incident as well as ongoing updates regarding any such incident until it has been addressed by the executive management leadership team. On an annual basis, the Board discusses the Company's approach to cybersecurity risk management with the Audit Committee members and management (including members of the Cybersecurity Committee). Throughout the year, the Board and its committees engage with management to discuss a wide range of enterprise risks related to the Company's businesses, including cybersecurity, and they confirm the alignment of risk assessment and mitigation with business strategy.

The Company regularly assesses and tests its cybersecurity policies, standards, processes, and practices, including, but not limited to, audits, tabletop exercises, threat modeling, and penetration and vulnerability testing. The Company regularly engages outside advisors and experts to anticipate future threats and trends and to perform assessments on our cybersecurity measures, including information security maturity assessments, audits, and independent reviews of our information security control environment and operating effectiveness. The results of such assessments, audits, and reviews are reported to the Cybersecurity Committee, Audit Committee and the Board, and the Company adjusts its cybersecurity policies, standards, processes, and practices as necessary based on the information provided by these assessments, audits, and reviews.

Cybersecurity Technical Safeguards

The Company invests in new information and cybersecurity services and technologies. Technical safeguards designed to protect the Company's information systems from cybersecurity threats include firewalls, continuous threat detection and response system(s), data leak prevention, enhanced email protection, antimalware functionality, and access controls, which are evaluated and improved through periodic assessments and cybersecurity threat intelligence.

Cybersecurity Incident Response and Recovery Planning

The Company has established and maintains incident response and data recovery plans that address the Company's response to a cybersecurity incident, and plans are reviewed by the Cybersecurity Committee and members of the IT department.

Third-Party Risk Management

The Company maintains a risk-based approach to identifying and overseeing risks from cybersecurity threats presented by third parties, including vendors, service providers, and other external users of the Company's systems as well as the systems of third parties that could adversely impact our business in the event of a cybersecurity incident affecting those third-party systems.

Education and Awareness

The Company provides regular training for personnel regarding cybersecurity threats as a means to equip the Company's personnel with effective tools to address cybersecurity threats and to communicate the Company's evolving information security policies, standards, processes, and practices.

Current Cybersecurity Risk Posture

To date, cybersecurity threats, including as a result of any previous cybersecurity incidents, have not materially affected the Company, including its business strategy, results of operations, or financial condition. However, as discussed under "Risk Factors" in Part I, Item 1A of this Annual Report on Form 10-K, cybersecurity threats pose multiple risks to us, including potentially to our results of operations and financial condition. For additional information concerning risks related to cybersecurity, see "Item 1A. Risk Factors - *Our business and operations would suffer in the event of system failures.*"

ITEM 2. PROPERTIES.

On February 21, 2023, we entered into a Sublease with Advance Magazine Publishers d/b/a Conde Nast for the entirety of the twenty-second floor of One Word Trade Center in New York, NY, or the Sublease. This space is utilized by the Company for its corporate and executive offices. The Sublease commenced on April 7, 2023 and was for ten (10) years. The Company had a one-time option to terminate the Sublease on its fifth anniversary upon the payment of a fee to the sublandlord.

On January 17, 2025, we entered into an Amendment to our Sublease (the "First Amendment"), pursuant to which we will relinquish our existing space in One World Trade Center and commence occupancy of different space within the building. The First Amendment extends the Sublease expiration date to January 31, 2036. We now have a one-time option to terminate the Sublease effective March 30, 2031 upon the payment of a fee to the sublandlord. The Company is responsible for base rent under the Sublease and certain additional customary variable costs, such as an allocable portion of building taxes and operating expenses. In connection with the Sublease and First Amendment, the Company received certain rent and work concessions from the sublandlord.

ITEM 3. LEGAL PROCEEDINGS.

Except as described herein, we, and our subsidiaries, are currently not a party to, and our property is not currently the subject of, any material pending legal proceedings; however, we may also become involved in various claims and legal actions arising in the ordinary course of business.

Securities Class Action

On May 13, 2022, Evy Gru filed a putative class action complaint captioned Gru v. Axsome Therapeutics, Inc., et al. in the U.S. District Court for the Southern District of New York, or the SDNY District Court, against the Company and certain of its current and former officers and one director, which we refer to as the Securities Class Action. The complaint asserts claims under Sections 10(b) and 20(a) of the Exchange Act and Rule 10b-5 promulgated thereunder, and alleges, among other things, that the defendants made false statements and omissions concerning the Company's Chemistry Manufacturing and Controls practices, and its NDA with the FDA, with respect to one of its product candidates, AXS-07. The named plaintiff sought unspecified damages, fees, interest, and costs. On August 11, 2022, the SDNY District Court appointed co-lead plaintiffs in the Securities Class Action, one of whom later withdrew. On October 7, 2022, the Securities Class Action plaintiffs filed an amended complaint, which contained substantially similar allegations as in the initial complaint. On September 25, 2023, the SDNY District Court granted defendants' motion to dismiss the amended complaint.

On October 13, 2023, plaintiffs' counsel filed a letter seeking leave to file an amended complaint and to substitute new plaintiffs, which defendants opposed. The SDNY District Court re-opened the lead plaintiff appointment process. Thomas Giblin, Paul Berger, and Paul Sutherland moved jointly to be appointed replacement plaintiffs. On January 22, 2024, the SDNY District Court granted that motion and ordered that the case name be changed to *In re Axsome Therapeutics, Inc. Securities Litigation*. On January 26, 2024, the replacement plaintiffs renewed their request for leave to file a proposed second amended complaint, and, on February 6, 2024, the SDNY District Court granted that request. Plaintiffs filed the second amended complaint on February 7, 2024. On March 11, 2024, the defendants moved to dismiss the second amended complaint.

Shareholder Derivative Action

On July 21, 2022, Daniel Engel filed a stockholder derivative complaint captioned Engel v. Herriot Tabuteau, et al. in the SDNY District Court against the Company's current directors, certain of the Company's current and former officers, and the Company (as nominal defendant). On January 27, 2023, Kyle Guterba filed a stockholder derivative complaint captioned Guterba v. Tabuteau, et al. in the SDNY District Court against the Company's current directors, certain of the Company's current and former officers, and the Company (as nominal defendant). The derivative complaints arise out of similar allegations as those made in the Securities Class Action. The plaintiffs assert claims for breach of fiduciary duties against all of the defendants and for contribution for violations of Section 10(b) and 21D of the Exchange Act. The plaintiffs seek unspecified damages, fees, interest, and costs, as well as corporate governance changes. The Engel and Guterba matters were consolidated on February 28, 2023 and are currently stayed pending further proceedings in the Securities Class Action.

Auvelity Paragraph IV Litigation

On March 24, 2023, we commenced a patent infringement action against Teva Pharmaceuticals, Inc., or Teva, relating to Teva's ANDA for Auvelity. This action is captioned *Axsome Therapeutics, Inc. and Antecip Bioventures II LLC v. Teva Pharmaceuticals, Inc.* No. 2:23-CV-01695 in the United States District Court for the District of New Jersey, or the NJ District Court. On December 15, 2023, we commenced a second patent infringement action against Teva relating to Teva's ANDA. This action is captioned *Axsome Therapeutics, Inc., and Antecip Bioventures II LLC v. Teva Pharmaceuticals, Inc.* No. 2:23-cv-23142 in the NJ District Court. On February 26, 2024, the NJ District Court consolidated the first and second actions. Fact discovery is currently scheduled to close on March 24, 2025 in the consolidated action. On May 28, 2024, we commenced a third patent infringement action against Teva relating to Teva's ANDA. This action is captioned *Axsome Therapeutics, Inc., and Antecip Bioventures II LLC v. Teva Pharmaceuticals, Inc.* No. 2:24-cv-06489 in the NJ District Court. On September 30, 2024, we commenced a fourth patent infringement action against Teva relating to Teva's ANDA. This action is captioned *Axsome Therapeutics, Inc., and Antecip Bioventures II LLC v. Teva Pharmaceuticals, Inc.* No. 2-24-cv-09535 in the NJ District Court. On December 5, 2024, we commenced a fifth patent infringement action against Teva relating to Teva's ANDA. The fifth action is captioned *Axsome Therapeutics, Inc., and Antecip Bioventures II LLC v. Teva Pharmaceuticals, Inc.* No. 2-24-cv-10938 in the NJ District Court. On January 7, 2025, the NJ District Court consolidated that third, fourth, and fifth actions.

On February 10, 2025, the Company announced that it had entered into a settlement agreement with Teva to resolve all outstanding litigation between the parties relating to Auvelity. Under the terms of the settlement agreement, Axsome will grant Teva a license to sell its generic version of Auvelity beginning on or after March 31, 2039, if pediatric exclusivity is granted for Auvelity, or on or after September 30, 2038, if no pediatric exclusivity is granted, subject to FDA approval and conditions and exceptions customary for agreements of this type.

Sunosi Paragraph IV Litigation

On September 13, 2023, we commenced a patent infringement action against Hikma and five other drug companies relating to each defendant's ANDA for Sunosi. This action is captioned *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Alkem Laboratories Ltd., et al*. No. 2:23-CV-20354 in the NJ District Court. We commenced related patent infringement actions against the defendants relating to their ANDAs on December 20, 2023, January 11, 2024, January 18, 2024, February 14, 2024, March 19, 2024 (2 actions filed), April 5, 2024, July 2, 2024, August 8, 2024, August 21, 2024, September 16, 2024, November 20, 2024 (4 actions filed), January 21, 2025. Those actions are captioned *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Unichem Laboratories Ltd*. No. 2:23-cv-23255; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Hetero USA, Inc. et al*. No 2:24-cv-00196; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Aurobindo Pharma USA, Inc. et al*. No. 2:24-cv-00309; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Sandoz, Inc*. No. 2:24-cv-00860; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Hetero USA, Inc. et al*. No 2:24-cv-03999; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Aurobindo Pharma USA, Inc. et al*. No. 2:24-cv-04002; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Alkem Laboratories Ltd., et al*. No. 2:24-CV-04608; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Aurobindo Pharma USA, Inc. et al*. No. 2-24-cv-07511; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Alkem Laboratories Ltd.*No. 2-24-cv-08365; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Aurobindo Pharma USA, Inc. et al.* No. 2-24-cv-08624; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Alkem Laboratories Ltd. et al*. No. 2-24-cv-09209; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Alkem Laboratories Ltd.* No. 2-24-cv-10617; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Hetero USA, Inc. et al*. No 2:24-cv-10618; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Aurobindo Pharma USA, Inc. et al*. No 2:24-cv-10619; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Hikma Pharmaceuticals USA Inc*. No 2:24-cv-10620; *Axsome Malta Ltd. & Axsome Therapeutics, Inc. v. Aurobindo Pharma USA, Inc. et al*. No 2:25-cv-00643, respectively, all of which are in the NJ District Court. On June 4, 2024, Axsome and the Malta Subsidiary entered into a settlement agreement with Unichem under which agreement Unichem agreed not to launch its generic solriamfetol product until June 30, 2042, or earlier under certain circumstances. On August 21, 2024, Axsome and the Malta Subsidiary reached an agreement to dismiss the actions pending against Sandoz. All other actions are currently pending. On September 25, 2024, Hikma Pharmaceuticals USA, Inc. filed a petition for Inter Partes Review of U.S. Patent No. 11,560,354 before the United States Patent and Trademark Office's Patent Trial and Appeal Board. That petition is captioned *Hikma Pharmaceuticals USA Inc. f/k/a West-Ward Pharmaceuticals Corp. v. Axsome Malta Ltd*. IPR2024-01418.

ITEM 4. MINE SAFETY DISCLOSURES.

Not applicable.

Part II

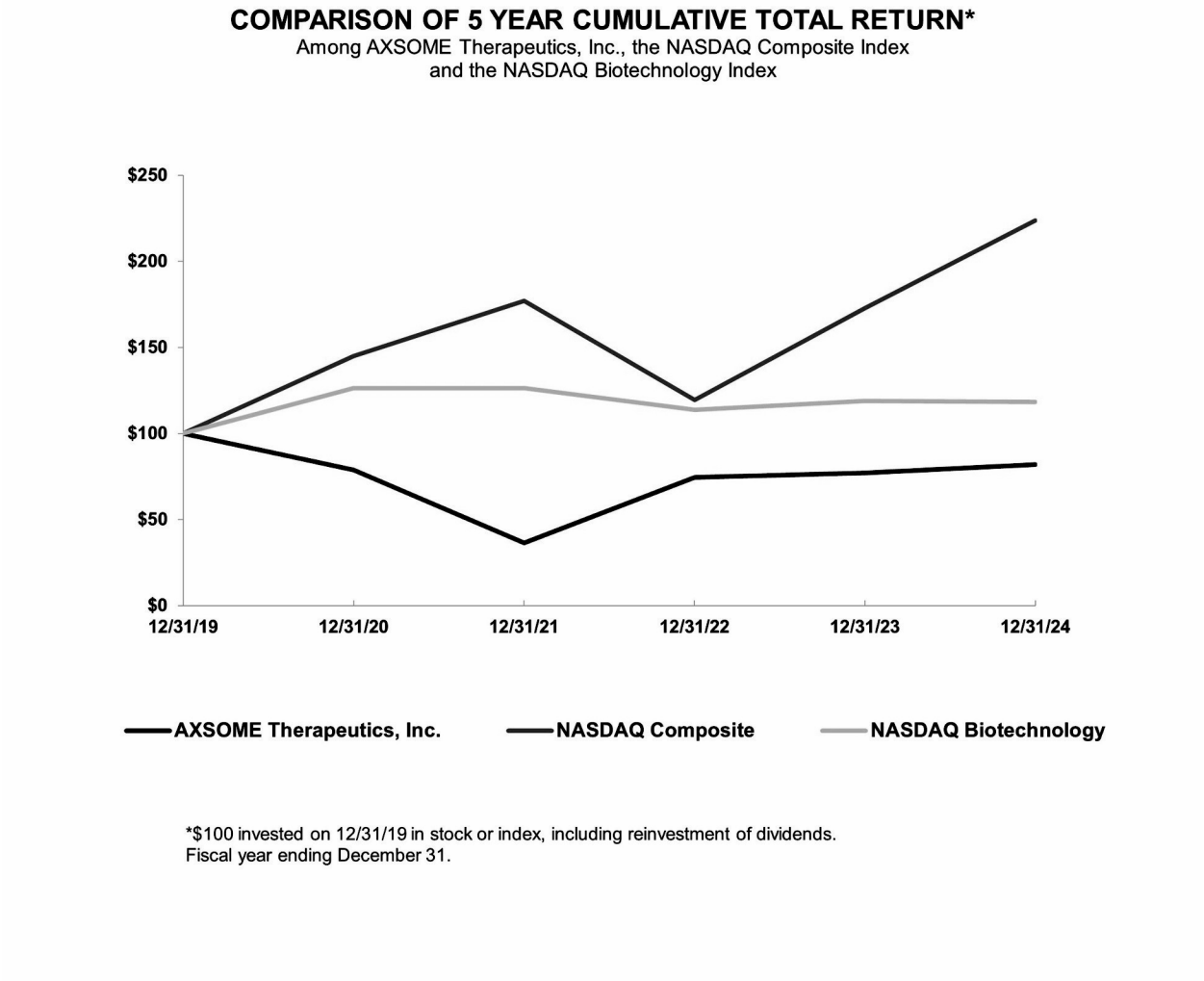
ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES.

Market Information

Our common stock has been listed on The Nasdaq Global Market since March 3, 2017, under the symbol "AXSM." Prior to that, our common stock was listed on The Nasdaq Capital Market since November 19, 2015, under the symbol "AXSM." Prior to our initial public offering, there was no public market for our common stock.

Common Stock Performance Graph

The graph below matches AXSOME Therapeutics, Inc.'s cumulative 5-Year total shareholder return on common stock with the cumulative total returns of the NASDAQ Composite index and the NASDAQ Biotechnology index. The graph tracks the performance of a $100 investment in our common stock and in each index (with the reinvestment of all dividends) from 12/31/2019 to 12/31/2024.



Holders

The number of record holders of our common stock as of February 11, 2025, was two. This number of holders of record does not reflect the beneficial holders of our common stock who hold shares in street name through brokerage accounts or other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities. The actual number of holders of our common stock is therefore greater than this number of record holders.

Dividends

We have never declared or paid any cash dividends on our common stock and do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be at the discretion of our Board, subject to applicable laws, and will depend on a number of factors, including our financial condition, results of operations, capital requirements, contractual restrictions, general business conditions, and any other factors that our Board may deem relevant. In addition, the terms of our existing term loan with Hercules precludes us from paying cash dividends without the consent of Hercules, except under certain circumstances.

ITEM 6. RESERVED

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis contain forward-looking statements about our plans and expectations of what may happen in the future. You should read the following discussion and analysis in conjunction with "Item 8. Financial Statements and Supplementary Data," and our consolidated financial statements beginning on page F-1 of this report. Forward-looking statements are based on a number of assumptions and estimates that are inherently subject to significant risks and uncertainties, and our results could differ materially from the results anticipated by our forward-looking statements as a result of many known or unknown factors, including, but not limited to, those factors discussed in "Item 1A. Risk Factors." See also the "Special Cautionary Notice Regarding Forward-Looking Statements" set forth at the beginning of this report.

Overview

We are a biopharmaceutical company leading a new era in the treatment of CNS disorders. We deliver scientific breakthroughs by identifying critical gaps in care and developing differentiated products with a focus on novel mechanisms of action that enable meaningful advancements in patient outcomes. Our CNS portfolio includes multiple FDA-approved products that are being further developed for additional neurological or psychiatric conditions and novel product candidates in late-stage clinical development. In May 2022, we completed the U.S. acquisition of Sunosi from Jazz and in November 2022, we acquired the ex-U.S. assets of Sunosi from Jazz for certain international markets. Sunosi is a product approved by the FDA and marketed in the U.S. to improve wakefulness in adult patients with EDS associated with narcolepsy or obstructive sleep apnea, and also approved in Europe in January 2020 by the European Commission. In August 2022, Auvelity® was approved by the FDA for the treatment of MDD in adults and we initiated the commercial launch of Auvelity in the U.S. in October 2022. In January 2025, Symbravo® was approved by the FDA for the acute treatment of migraine with or without aura in adults. Refer to Part I, Item 1. "Business" for a summary of our clinical programs.

Since our incorporation in January 2012, our operations to date have included organizing and staffing our company, business planning, raising capital, developing our compounds, engaging in other discovery and preclinical activities, the commercial launches of Auvelity and Sunosi, and preparatory activities for the launch of Symbravo. Subsequent to our IPO, we financed our operations primarily through proceeds from sales of our common stock to equity investors and debt borrowings. For a further discussion, see the section entitled "Liquidity and Capital Resources" below.

Our ability to become profitable depends on our ability to generate revenue. We have recently begun commercial sales of Auvelity and Sunosi, and plan to commercially launch Symbravo, but we have limited experience with commercializing these, or any, products.

We have incurred significant operating and net losses since inception. We incurred net losses of $287.2 million and $239.2 million for the years ended December 31, 2024 and 2023, respectively. Our accumulated deficit as of December 31, 2024 was $1,122.8 million, and we expect to incur significant expenses and continuing operating losses. We expect our expenses to increase in connection with our ongoing activities, as we continue the commercialization of our on-market products and the development and clinical trials of, and seek regulatory approval for, our current product candidates and any other product candidates that we develop or in-license and advance to clinical development. Further, we have incurred and will continue to incur additional costs associated with operating as a public company. Accordingly, we may need additional financing to support our continuing operations. We may seek to fund our operations through public or private equity, debt financings, or other sources. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy. We will need to generate significant revenue to achieve profitability, and we may never do so.

Financial Overview

Revenue

We generated $381.7 million and $202.5 million in net revenue from product sales for the years ended December 31, 2024 and 2023, respectively.

We expect that Auvelity, Sunosi, and Symbravo revenues are likely to fluctuate based on demand quarter to quarter. We will not generate revenue from other products unless and until we successfully develop, obtain regulatory approval of, and commercialize one of our current or future product candidates. We have incurred significant operating losses since inception. If we fail to complete the development of our product candidates in a timely manner or obtain regulatory approval for them, our ability to generate future revenue from such product candidates, and our results of operations and financial position, would be materially and adversely affected. If we enter into licensing or collaboration arrangements, such agreements may or may not generate revenue in the future.

Additionally, in the fourth quarter of 2024, we recorded a milestone revenue of $0.5 million related to an achievement of a regulatory milestone in China for Sunosi from SK. In the first quarter of 2023, we recorded license revenue of $65.7 million related to the Pharmanovia License Agreement (as defined below). See below for more detail.

License Agreement with Pharmanovia

In February 2023, we entered into the Pharmanovia License Agreement with Pharmanovia to commercialize and further develop Sunosi® in the Territory. Pharmanovia is a UK-based global life cycle management healthcare company that focuses on four core therapeutic areas – Oncology, Endocrinology, Neurology and Cardiovascular.

We received an upfront payment of €62.0 million ($65.7 million) during the first quarter of 2023 and are eligible to receive sales-based and other milestone payments totaling up to €94.5 million. We will receive a royalty percentage in the mid-twenties on net sales of the Licensed Products (as defined in the Pharmanovia License Agreement) in the Territory. For the year ended December 31, 2024, we recognized royalty revenue of $3.5 million related to Pharmanovia's sales of Sunosi.

Cost of revenue

Cost of revenue includes direct costs of formulating, manufacturing, and packaging drug product, overhead costs consisting of labor, customs, stock-based compensation, shipping, outside inventory management, royalty expense, and other miscellaneous operating costs. In the fourth quarter of 2024, we recorded a $2.5 million expense for the achievement of a sales-based milestone related to world-wide Sunosi sales. In the first quarter of 2023, we recorded a $5.0 million license sharing expense related to the upfront license revenue received.

Research and development expenses

Research and development expenses primarily include preclinical studies, clinical trials, manufacturing costs, employee-related expenses including salaries, benefits, travel, and stock based compensation expense, contract services, including external research and development expenses incurred under arrangements with third parties, such as CROs, facilities costs, overhead costs, depreciation, and other related costs.

Research and development activities are central to our business model. We have and will incur substantial costs beyond our present and planned clinical trials in order to file an NDA for any of our product candidates. It is difficult to determine with certainty the costs and duration of our current or future clinical trials and preclinical studies, or to what extent we will generate revenue from the commercialization and sale of Auvelity, Sunosi, and Symbravo or our product candidates if we obtain regulatory approval. The duration, costs, and timing of clinical trials and development of our product candidates will depend on a variety of factors, including the uncertainties of future clinical trials and preclinical studies, uncertainties in clinical trial enrollment rate, and significant and changing government regulation. In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability, and commercial viability. We will determine which programs to pursue and how much to fund each program in response to the scientific and clinical success of each product candidate, as well as an assessment of each product candidate's commercial potential.

Selling, general and administrative expenses

Selling, general and administrative expenses primarily consist of salaries and related costs for personnel in executive, commercial, finance, and operational functions, including stock-based compensation and travel expenses. Also included in selling, general and administrative expenses are marketing costs, other commercial costs, pre-commercialization costs, facility-related costs, insurance expense, professional fees for legal and accounting services, and patent filing and prosecution costs. Selling, general and administrative expenses are expensed when incurred.

Interest expense, net

Interest expense, net, primarily consists of cash interest and non-cash costs related to our term loans (see "Liquidity and Capital Resources" below for a further discussion). We amortize these costs over the term of our debt agreements as interest expense in our consolidated statement of operations. Interest expense, net also includes interest income earned on cash and cash equivalents.

Intangible asset amortization

The intangible asset is amortized using the straight-line method over its estimated period of benefit of ten years. We evaluate recoverability of the intangible asset periodically by considering events or changes in circumstances that may warrant revised estimates of useful life or that indicate the asset may be impaired.

Fair value in contingent consideration

Consideration paid in a business combination may include potential future payments that are contingent upon the acquired business achieving certain milestones in the future ("contingent consideration"). The royalty payments due to Jazz are a high single-digit royalty on our U.S. net sales of Sunosi in the current indication and a mid single-digit royalty on our U.S. net sales of Sunosi for future indications. Contingent consideration liabilities are measured at their estimated fair value as of the date of acquisition, with subsequent changes in fair value recorded in the consolidated statements of operations during such period a change is recognized. We estimate the fair value of the contingent consideration as of the acquisition date and reporting periods thereafter using the estimated future cash outflows based on future sales.

Critical Accounting Policies and Significant Judgments and Estimates

This discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States of America ("GAAP"). The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of expenses during the reported period. In accordance with GAAP, we base our estimates on historical experience and on various other assumptions that we believe are reasonable under the circumstances. Actual results may differ from these estimates under different assumptions or conditions.

Management considers many factors in developing the estimates and assumptions that are used in the preparation of our consolidated financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of the ultimate future outcomes, and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made.

While our significant accounting policies are more fully described in Note 2 to our audited consolidated financial statements appearing elsewhere in this report, we believe the following accounting policies are critical to the judgments and estimates we use in the preparation of our consolidated financial statements.

Revenue Recognition

Revenues from product sales are recorded at the net sales price, which includes estimates of variable consideration that result from: invoice discounts for prompt payment and distribution service fees, government rebates, PBMs and Managed Care Organization rebates, chargebacks, discounts and fees, product returns and costs of co-pay assistance programs for patients. Reserves are established for the estimates of variable consideration based on the amounts earned or to be claimed on the related sales. The reserves are classified as reductions to Accounts receivable, net or accrued expenses and other current liabilities. Our estimates of variable consideration and determination of whether to include estimated amounts in the transaction price are based largely on an assessment of its anticipated performance and all information (historical, current, and forecasted) that is reasonably available. These reserves reflect our best estimate of the amount of consideration to which we are entitled to based on the terms of the contracts.

We make significant estimates and judgments that materially affect our recognition of net product revenue. Claims by third parties for rebates, chargebacks and discounts frequently are submitted to us significantly after the related sales, potentially resulting in adjustments in the period in which the new information becomes known. Rebates apply to: Medicaid, managed care, and supplemental rebates to all applicable states as defined by the statutory government pricing calculation requirements under the Medicaid Drug Rebate Program. Tricare rebates to the TRICARE third-party administrator are based on the statutory calculation defined in the agreement with the Defense Health Agency. Part D and Commercial Managed Care rebates are paid based on the contracts with PBMs and Managed Care Organizations. Rebates are paid to these entities upon receipt of an invoice from the contracted entity, which is based on the utilization of the product by the members of the contracted entity We estimate these rebates and records such estimates in the same period the related product sales is recognized, resulting in a reduction to product sales as well as a component of accrued expenses and other current liabilities. We will adjust our estimates based on new information, including information regarding actual rebates, chargebacks and discounts for our products, as it becomes available.

License revenue

We generate revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain products. Such agreements may include the transfer of intellectual property rights in the form of licenses. Payments made by the customer may include non-refundable upfront fees, payments based upon the achievement of defined milestones, and royalties on sales of products.

If a license to the intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, we recognize the transaction price allocated to the license as revenue upon transfer of control of the license. All other promised goods or services in the agreement are evaluated to determine if they are distinct. If they are not distinct, they are combined with other promised goods or services to create a bundle of promised goods or services that is distinct. Optional future services where any additional consideration paid to us reflects their standalone selling prices do not provide the customer with a material right and, therefore, are not considered performance obligations. If optional future services are priced in a manner which provides the customer with a significant or incremental discount, they are material rights and are accounted for as separate performance obligations.

Contingent milestones at contract inception are estimated to the extent that it is probable that a significant revenue reversal would not occur and included in the transaction price using the most likely amount method. Milestone payments that are not within our control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received, and, therefore, the variable consideration is constrained. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which we recognize revenue as or when the performance obligations under the contract are satisfied. At the end of each reporting period, we re-evaluate the probability of achieving development or sales-based milestone payments that a significant revenue reversal would not occur and, if necessary, adjust the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license and other revenue, as well as earnings, in the period of adjustment.

For arrangements that include sales-based royalties, including sales-based milestone payments, and a license of intellectual property that is deemed to be the predominant item to which the royalties relate, revenue is recognized at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalties have been allocated has been satisfied (or partially satisfied).

Research and development expenses

Research and development costs are expensed as incurred. Research and development expenses consist primarily of personnel costs for our research and development employees, costs incurred to third-party service providers for the conduct of research, preclinical and clinical studies, laboratory supplies, product license fees, consulting and other related expenses. We estimate research, preclinical and clinical study expenses based on services performed, pursuant to contracts with third-party research and development organizations that conduct and manage research, preclinical and clinical activities on our behalf. We estimate these expenses based on reviewing contracts, vendor agreements, discussions with internal management personnel and external service providers as to the progress or stage of completion of services and the contracted fees to be paid for such services. If the actual timing of the performance of services or the level of effort varies from the original estimates, we will adjust the accrual accordingly. Payments associated with licensing agreements to acquire licenses to develop, use, manufacture and commercialize products that have not reached technological feasibility and do not have alternative future use are expensed as incurred.

Goodwill

Goodwill is deemed to have an indefinite life and therefore not amortized. We test the carrying amounts of goodwill for recoverability on an annual basis or more frequently if events or changes in circumstances indicate that the asset might be impaired. When reviewing goodwill for impairment, we first evaluate the qualitative factors to determine whether it is more likely than not that the fair value of a reporting unit is less than its carrying amount. The qualitative assessment involves consideration of factors including macroeconomic conditions, conditions specific to the industry, external cost factors that could have a significant effect on earnings or cash flows, all of which requires significant judgment. If the qualitative factors determine it is necessary to complete a goodwill impairment test, the fair value of the relevant reporting unit is determined and compared to its carrying value. If the fair value is greater than the carrying value, then the carrying value is deemed to be recoverable, and no further action is required. If the fair value estimate is less than the carrying value, goodwill is considered impaired for the amount by which the carrying amount exceeds the reporting unit's fair value, and a charge is reported in impairment of goodwill in our consolidated statements of operations. As of December 31, 2024, we determined that we have one reporting unit. We have not identified any events or changes in circumstances that indicate the existence of potential impairment of goodwill during the year ended December 31, 2024.

Intangible asset

The intangible asset is amortized using the straight-line method over its estimated period of benefit of ten years. We evaluate recoverability of the intangible asset periodically by considering events or changes in circumstances that may warrant revised estimates of useful lives or that indicate the asset may be impaired. When impairment indicators are present, we assess the undiscounted projected cash flow for the asset and compare this estimated amount to carrying amount. If the carrying amount is greater, we record an impairment loss for the amount equal to the excess carrying amount over fair value. Due to the nature of estimating project cash flows for an asset, there is significant judgment involved in determining the fair value of an intangible asset. We have not identified any events or changes in circumstances that indicate the existence of potential impairment of the intangible asset during the year ended December 31, 2024.

Contingent consideration

Consideration paid in a business combination may include contingent consideration. In connection with the Acquisition, we have obligations to make royalty payments to Jazz in the high single-digits on our U.S. net sales of Sunosi in the current indication and a mid single-digit royalty on our U.S. net sales of Sunosi for future indications. We estimate fair value of contingent consideration liabilities using the probability weighted income approach as of the date of acquisition, with subsequent changes in fair value recorded in the consolidated statements of operations during such period a change is recognized. During each reporting period, significant assumptions are required in determining fair value, including estimating the future sales of Sunosi in current and future indications, timing of regulatory and commercial milestone achievements, probability of technical and regulatory success rates, and discount rates. Significant judgment is used in assessing the appropriateness of these assumptions as one or more may involve inputs that are not observable in the market. Accordingly, changes in the assumptions may have a material impact on the change in fair value of contingent consideration liabilities recorded in any given period.

The fair value measurement of the contingent consideration is sensitive to the change in discount rates. As of December 31, 2024, if the discount rate increases or decreases by approximately 1%, the fair value of the contingent consideration would range from $91.5 million to $104.5 million. As of December 31, 2024, if the revenue discount rate increases or decreases by approximately 1%, the fair value of the contingent consideration would range from $92.9 million to $102.9 million.

Income taxes

Income taxes are accounted for under the asset and liability method. Under this method, deferred tax assets and liabilities are recognized for the future tax consequences attributable to the differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases, operating losses, and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period that includes the enactment date. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

We recognize the tax benefit from an uncertain tax position only if it is more likely than not to be sustained upon examination based on the technical merits of the position as well as consideration of the available facts and circumstances. When uncertain tax positions exist, we recognize the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. As of December 31, 2024, we do not believe any material uncertain tax positions are present.

As of December 31, 2024, we had U.S. federal net operating loss carryforwards of approximately $572.1 million and foreign NOL carryforwards of $4.8 million. U.S. federal NOLs amounting to $59.8 million generated before the 2018 tax year will start expiring beginning 2032, and the NOLs of approximately $512.3 million generated in 2018 and later have an indefinite carryforward period.

Utilization of the NOLs may be subject to a substantial annual limitation due to ownership change limitations provided by the Internal Revenue Code of 1986, as amended. The annual limitation for net operating losses incurred before the 2018 tax year may result in expiration before we can use them. We have recorded a valuation allowance on all of our deferred tax assets.

Stock-based compensation

For issued stock options, we estimate the grant date fair value of each option using the Black-Scholes option pricing model. The Black-Scholes model requires management to make assumptions, including expected volatility of our common stock, the risk-free interest rate, the expected term of the option, the fair value of our common stock, expected dividend yield, and the exercise price. Certain assumptions utilized in the Black-Scholes calculation involve a number of variables, uncertainties, and application of management judgment that are inherently subjective. Significant changes in these assumptions can materially affect the fair value and ultimately the amount of stock-based compensation expense that is recognized.

We recognize the grant date fair value of the stock options over the requisite service period, which is generally the vesting term. For awards only subject to service-based vesting conditions, we elected to recognize stock-based compensation expense on a straight-line basis.

Results of Operations

Comparison of the Years Ended December 31, 2024 and 2023

The following table summarizes our results of operations for the years ended December 31, 2024 and 2023 (in thousands, except share and per share amounts):

	Year ended December 31,	
	2024	2023
Revenues:		
Product sales, net	$ 381,677	$ 202,460
License revenue	—	65,735
Royalty and milestone revenue	4,016	2,405
Total revenues	385,693	270,600
Operating expenses:		
Cost of revenue (excluding amortization and depreciation)	33,303	26,065
Research and development	187,077	97,944
Selling, general and administrative	411,359	323,123
Loss in fair value of contingent consideration	28,124	48,918
Intangible asset amortization	6,392	6,375
Total operating expenses	666,255	502,425
Loss from operations	(280,562)	(231,825)
Interest expense, net	(6,569)	(6,453)
Loss before income taxes	(287,131)	(238,278)
Income tax expense	(85)	(960)
Net loss	$ (287,216)	$ (239,238)
Net loss per common share, basic and diluted	$ (5.99)	$ (5.27)
Weighted average common shares outstanding, basic and diluted	47,914,253	45,425,212

Product sales, net. Auvelity U.S. net sales were $291.4 million and $130.1 million for the years ended December 31, 2024 and 2023, respectively. Sunosi net sales were $90.3 million and $72.4 million for the years ended December 31, 2024 and 2023, respectively. The increases were primarily due to the increase in unit sales volume for both Auvelity and Sunosi.

The following table summarizes the activity of our sales allowance and reserves as of and for the year ended December 31, 2024 (in thousands):

	Commercial discounts and rebates, returns and other	Cash discounts and chargebacks	Medicaid and Medicare rebates	Total
Balance at December 31, 2023	$ 37,492	$ 12,501	$ 9,222	$ 59,215
Provisions	239,549	97,169	41,277	377,995
Payments/credits	(221,629)	(96,166)	(31,961)	(349,756)
Balance at December 31, 2024	$ 55,412	$ 13,504	$ 18,538	$ 87,454

License revenue. In February 2023, we entered into the Pharmanovia License Agreement to commercialize Sunosi in certain ex-U.S. markets. We recognized the upfront payment of $65.7 million from Pharmanovia as license revenue during the first quarter of 2023. We did not have license revenue during the year ended December 31, 2024.

Royalty and milestone revenue. In connection with the February 2023 Pharmanovia License Agreement to commercialize Sunosi in certain ex-U.S. markets, we recognized royalty revenue of $3.5 million for the year ended December 31, 2024, as compared to $2.4 million for the year ended December 31, 2023 attributable to Pharmanovia sales of Sunosi in the out-licensed markets. The increase was in line with the increase in unit sales volume of Sunosi in certain ex-U.S. markets. Further, in the fourth quarter of 2024, we recognized milestone revenue of $0.5 million related to an achievement of a regulatory milestone in China for Sunosi from SK.

Cost of revenue. Cost of revenue was $33.3 million for the year ended December 31, 2024, as compared to $26.1 million for the year ended December 31, 2023. The increase was in line with the increase in sales of Auvelity and Sunosi. Cost of revenue for the year ended December 31, 2024 includes a $2.5 million expense for the achievement of a sales-based milestone related to world-wide Sunosi sales. Additionally, cost of revenue for the year ended December 31, 2023 includes a $5.0 million license sharing expense related to the Pharmanovia License Agreement.

Research and development. The following table summarizes our research and development expenses for our primary products for the years ended December 31, 2024 and 2023 (in thousands):

	Year ended December 31,	
	2024	2023
Solriamfetol	$ 53,678	$ 18,232
AXS-05	62,877	34,011
AXS-07	15,587	8,101
AXS-12	9,362	10,431
AXS-14	11,881	7,091
Other research and development (*)	12,274	5,998
Stock-based compensation	21,418	14,080
Total research and development expenses	$ 187,077	$ 97,944

(*) Other research and development expenses primarily consist of facilities charges, third party consultant costs, costs related to other product candidates, and other unallocated costs.

Research and development expenses increased by $89.2 million for the year ended December 31, 2024, as compared to the year ended December 31, 2023. The increase was primarily related to the Phase 3 trials for additional indications, including studies in ADHD, MDD, BED, and SWD, for solriamfetol, the advancement of ongoing Phase 3 trials of AXS-05 and AXS-12, higher manufacturing costs for AXS-07 and AXS-14, and higher personnel costs due to organizational growth. Research and development expenses are expected to stabilize at current levels in the near term as certain development programs near completion while new development programs are initiated.

Selling, general and administrative. Selling, general and administrative expenses were $411.4 million for the year ended December 31, 2024, as compared to $323.1 million for the year ended December 31, 2023. The increase was primarily related to greater commercial activities for Auvelity and Sunosi, and higher personnel costs related to organizational growth, including non-cash stock-based compensation. We expect selling, general and administrative expenses to increase as we expand marketing, promotional, and advertising costs for Auvelity and Sunosi, launch Symbravo, and to support general administrative needs.

Loss in Fair Value of Contingent Consideration. The $28.1 million change for the year ended December 31, 2024, as compared to a $48.9 million change for the year ended December 31, 2023 was primarily related to changes in significant unobservable inputs, including discount rates, and significant assumptions, including future sales estimates.

Intangible asset amortization. We amortize the intangible asset, which we recognized as part of the Acquisition, over its useful life of 10 years. Intangible asset amortization was $6.4 million for both the years ended December 31, 2024 and 2023.

Interest expense, net. Interest expense, net, was $6.6 million for the year ended December 31, 2024 as compared to $6.5 million for the year ended December 31, 2023. The increase was mainly due to an increase in interest expense related to the Loan Agreement and non-cash interest expense on leases, offset by additional interest income from higher interest rates on cash balances.

Income tax expense. We recorded an income tax expense of $0.1 million for the year ended December 31, 2024 due to state taxes that we expect to pay based on minimum tax requirements in various states. We recorded a tax expense of $1.0 million for the year ended December 31, 2023 due to income earned in Malta in relation to the license revenue recognized from the Pharmanovia License Agreement.

Net loss. Net loss for the year ended December 31, 2024 was $287.2 million as compared to $239.2 million for the year ended December 31, 2023. The increase was primarily due to higher research and development spend from pre-clinical and ongoing clinical trial expenses, higher selling, general and administrative expenses from commercial activities related to Auvelity and Sunosi, including sales force and marketing spend, and higher personnel costs due to organizational growth, including non-cash stock compensation expense. Additionally, the increase in net loss was impacted by the upfront payment of $65.7 million received from Pharmanovia in the first quarter of 2023.

Liquidity and Capital Resources

Since our inception through December 31, 2024, we have financed our operations primarily through proceeds from equity offerings, debt borrowings, and proceeds from product sales. See discussion below.

On December 2, 2022, we filed an automatic shelf registration statement with the SEC for the issuance of common stock, preferred stock, warrants, rights, debt securities, and units up to an unlimited amount, which we refer to as the 2022 Shelf Registration Statement. It was declared effective by the SEC upon filing. In the future, we may conduct additional offerings of one or more of these securities utilizing the 2022 Shelf Registration Statement in such amounts, prices and terms to be announced when and if the securities are offered. At the time any of our securities covered by the 2022 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of any such offering.

In December 2019, we entered into a sales agreement, or the December 2019 Sales Agreement, with SVB Securities LLC (now known as Leerink Partners LLC), or Leerink, pursuant to which we may sell up to $80 million in shares of our common stock from time to time through Leerink, acting as our sales agent, in one or more at-the-market offerings utilizing an automatic shelf registration statement we filed with the SEC on December 5, 2019 for the issuance of common stock, preferred stock, warrants, rights, debt securities and units up to an unlimited amount, which we refer to as the 2019 Shelf Registration Statement. Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the December 2019 Sales Agreement.

In March 2022, we entered into a sales agreement, or the March 2022 Sales Agreement with Leerink, and filed a prospectus supplement, pursuant to which we may sell up to $200 million in shares of our common stock from time to time through Leerink, acting as our sales agent, in one or more at-the-market offerings utilizing the 2019 Shelf Registration Statement. Leerink is entitled to receive a commission of up to 3.0% of the gross proceeds for any shares sold under the March 2022 Sales Agreement. The March 2022 Sales Agreement supersedes the December 2019 Sales Agreement, by and between us and Leerink. We exhausted sales of shares of our common stock under our prior at-the-market offering program.

In August 2022, we filed a prospectus supplement to the 2019 Shelf Registration Statement for the issuance and sale, if any, of up to an additional $250 million in shares of our common stock. Leerink is entitled to receive a commission of up to 3.0% of the gross proceeds for any shares sold under the March 2022 Sales Agreement.

In December 2022, in connection with the 2022 Shelf Registration Statement, we filed a new sales agreement prospectus to replace the prior prospectus supplement filed in August 2022 associated with the expired 2019 Shelf Registration Statement. The new sales agreement prospectus covered the issuance and sale by us of up to the same $250 million of our common stock that may be issued and sold from time to time through Leerink, as the sales agent, under the March 2022 Sales Agreement.

For the year ended December 31, 2024, we received approximately $40.8 million in gross proceeds through the sale of 466,108 shares, of which net proceeds were approximately $40.0 million, under the March 2022 Sales Agreement. We did not utilize the March 2022 Sales Agreement with Leerink during the year ended December 31, 2023.

In January 2023, we entered into a Third Amendment to the Loan Agreement, or the Third Amendment, with Hercules. The Third Amendment increased the size of the Term Loan Advance (as defined in the Loan Agreement) to $350.0 million, reduces the interest rate, and extends the maturity and interest-only period of the Loan Agreement. In September 2024, we entered into a Fifth Amendment to the Loan Agreement, or the Fifth Amendment, with Hercules. The Fifth Amendment amended the terms of the Loan Agreement to, among other things: (i) increase the size of the aggregate principal amount under tranche 3 of the 2020 Term Loan (as defined below) from $75.0 to $80.0 million; (ii) extend the availability periods of certain tranches of the 2020 Term Loan; (iii) alter the terms of the performance covenants contained in the Loan Agreement and also add a new performance covenant; (iv) conditionally waive the minimum cash requirement during such periods of time that Axsome's market capitalization exceeds $1.5 billion; and (v) permit Axsome Malta Ltd., or the Malta Subsidiary, to request an advance from the Lenders (as defined in the Loan Agreement) up to a certain amount to the extent that Axsome may request an advance in such amount and to increase the amount of cash that the Malta Subsidiary may hold outside of the United States, as set forth in greater detail in the Fifth Amendment. We drew down upon tranche 1C of the 2020 Term Loan, and as of December 31, 2024, we had approximately $180 million outstanding and $150 million remaining under the 2020 Term Loan. See the "Contractual Obligations and Commitments – January 2023 Third Amendment to the Loan and Security Agreement – Hercules", "Contractual Obligations and Commitments – September 2024 Fifth Amendment to the Loan and Security Agreement – Hercules" sections below, and Note 10. Loan and Security Agreement for more information.

In June 2023, we completed an underwritten public offering of our common stock and sold 3.0 million shares of our common stock at a public offering price of $75.00 per share. Net proceeds were $211.3 million, net of underwriting discounts and commissions of $13.5 million and other offering costs of $0.2 million. Additionally, in connection with this public offering, in July 2023, the underwriters fully exercised their option to purchase 450,000 additional shares of our common stock, at a public offering price of $75.00 per share. The net proceeds were $31.7 million, net of underwriting discounts and commissions of $2.0 million and other minimal offering costs.

In the future, we may conduct additional offerings of one or more of the securities covered by the 2022 Shelf Registration Statement in such amounts, prices and terms to be announced when and if the securities are offered. At the time any of our securities covered by the 2022 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of any such offering.

On February 21, 2023, we entered into a Sublease with Advance Magazine Publishers d/b/a Conde Nast for the entirety of the twenty-second floor of One Word Trade Center in New York, NY, or the Sublease. This space is utilized as our corporate and executive offices. The Sublease commenced on April 7, 2023 and will run for ten (10) years. We have a one-time option to terminate the Sublease on its fifth anniversary upon the payment of a fee to the sublandlord. We are responsible for base rent under the Sublease and certain additional customary variable costs such as an allocable portion of building taxes and operating expenses. In connection with the Sublease, we received certain rent and work concessions from the sublandlord. The Company entered into a fleet lease program beginning the first quarter of 2024. The lease agreement includes an initial 12-month noncancelable period with monthly renewal options thereafter. Lease terms range from approximately 40 to 50 months and are classified as finance leases. See Note 11. Commitments and Contingencies for further information on future contractual obligations.

We believe that our current cash is sufficient to fund anticipated operations into cash flow positivity, based on the current operating plan. Because the process of commercializing products and evaluating product candidates in clinical trials is costly and the timing of progress in these trials is uncertain, it is possible that the assumptions upon which we have based this estimate may prove to be wrong, and we could use our capital resources sooner than we currently expect.

Cash Flows

The following table summarizes our primary sources and uses of cash for the periods indicated (in thousands):

	Year ended December 31,	
	2024	2023
Net cash (used in) provided by:		
Operating activities	$ (128,410)	$ (145,080)
Investing activities	(270)	(582)
Financing activities	57,840	331,013
Net increase (decrease) in cash	$ (70,840)	$ 185,351

Operating Activities. Cash used in operating activities for the year ended December 31, 2024 was $128.4 million as compared to $145.1 million for the year ended December 31, 2023. The decrease of $16.7 million was mainly due to higher net product revenues from Auvelity and Sunosi in 2024, which was offset by the increase in cash used in commercial and clinical activities in 2024. Operating activities in 2023 also was impacted by the receipt of a $65.7 million upfront payment from Pharmanovia in the first quarter of 2023.

Investing Activities. Cash used in investing activities for the year ended December 31, 2024 was $270 thousand, as compared to $582 thousand for the year ended December 31, 2023. The decrease was impacted by the expansion of our corporate headquarters during 2023.

Financing Activities. Cash provided by financing activities was $57.8 million for the year ended December 31, 2024, which included net proceeds of $40.0 million from issuance of common stock for financing purposes as well as proceeds of $30.7 million from the issuance of common stock upon the exercise of employee stock options and under the ESPP, which was partially offset by payments of contingent consideration and tax withholdings on stock awards, for a total of $11.8 million. Cash provided by financing activities was $331.0 million for the year ended December 31, 2023, which included net proceeds related to the June 2023 public offering of $211.3 million and additional net proceeds of $31.7 million as the underwriters fully exercised their option to purchase additional shares, net proceeds of $83.6 million from draw-downs related to the Loan Agreement with Hercules, and proceeds of $12.4 million from the issuance of common stock upon the exercise of employee stock options, offset by payments of contingent consideration and tax withholdings on stock awards for a total of $8.0 million.

Funding Requirements

We have not achieved profitability since our inception, and we expect to continue to have losses as we continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercially launch Symbravo while further investing in Auvelity and Sunosi. We are subject to all of the risks pertinent to the development of new product candidates, and we may encounter unforeseen expenses, difficulties, complications, delays, and other unknown factors that may harm our business.

We may need to raise additional financing in the future to fund our operations. In the event that we need additional financing, we may incur additional debt, license certain intellectual property, and seek to sell additional equity or convertible securities that may result in dilution to our stockholders. If we raise additional funds through the issuance of equity or convertible securities, these securities could have rights or preferences senior to those of our common stock and could contain covenants that restrict our operations. There can be no assurance that we will be able to obtain additional equity or debt financing on terms acceptable to us, if at all. Our future capital requirements will depend on many factors, including:

- the scope, rate of progress, results, and cost of our clinical studies and other related activities;
- our ability to enter into collaborative agreements for the development and commercialization of our product candidates;

- the number and development requirements of any other product candidates that we pursue;
- the costs, timing, and outcome of regulatory reviews of our product candidates;
- the costs and timing of our commercialization activities, including product manufacturing, marketing, sales, and distribution, for any of our products and product candidates for which we receive marketing approval;
- any product liability or other lawsuits related to our product candidates;
- the expenses needed to attract and retain skilled personnel;
- the general and administrative expenses related to being a public company;
- the revenue received from commercial sales of our products and product candidates for which we receive marketing approval; and
- the costs involved in preparing, filing, and prosecuting patent applications, maintaining and enforcing our intellectual property rights, and defending our intellectual property-related claims.

Please see "Risk Factors" for additional risks associated with our substantial capital requirements.

Contractual Obligations and Commitments

License agreement with Pfizer

In January 2020, we entered into a license agreement with Pfizer. Under the terms of our exclusive license agreement with Pfizer, Pfizer received 82,019 shares of our common stock having a stated value of $8.0 million, based on the average closing price of our common stock for the ten prior trading days of $97.54, in consideration for the license and rights. Pfizer also received an upfront cash payment of $3.0 million. We determined that the fair value of each share of common stock granted to Pfizer on the closing date of January 9, 2020 was $87.24, based on the closing price of our common stock on that date. As a result, the fair value of the stock issued was $7.2 million.

Pfizer can also receive up to $323 million upon the achievement of certain regulatory and sales milestones, and tiered mid-single to low double-digit royalties on future sales of any such approved clinical products containing compounds reboxetine esreboxetine. Pfizer will also have a right of first negotiation on any potential future strategic transactions involving AXS-12 and AXS-14.

License agreements with Antecip Bioventures

Under three exclusive license agreements with Antecip an entity owned by our Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., we are obligated to make specified royalty payments ranging from 1.5% to 4.5%, subject to up to a 50% reduction depending on required payments to third parties, on net sales of our products containing the licensed technology of AXS-02, AXS-05, and AXS-04.

In connection with the Loan Agreement (see below), Antecip consented to the collateral assignment of one of the license agreements, among other things, under a direct agreement with us and Hercules.

Loan and Security Agreement with Hercules Capital, Inc.

Capitalized terms used but not otherwise defined herein shall have the meanings assigned to them in the Loan Agreement.

September 2024 Fifth Amendment to the Loan and Security Agreement

On September 30, 2024, we entered into the Fifth Amendment. The Fifth Amendment amended the terms of the Loan Agreement to, among other things: (i) increase the Tranche 3 Commitment from $75.0 to $80.0 million; (ii) extend the availability periods of Tranche 1D to June 15, 2025 and that of Tranche 1E to December 15, 2025, as set forth in greater detail in the Fifth Amendment; (iii) alter the terms of Performance Covenant A, Performance Covenant B, and Performance Covenant C and also add a Performance Covenant D, as set forth in greater detail in the Fifth Amendment; (iv) conditionally waive the requirement that the Company maintain Qualified Cash in an amount greater than or equal to the sum of $30.0 million plus the Qualified Cash A/P Amount at all times during such periods of time that the Company's Market Capitalization exceeds $1.5 billion; and (v) permit the Malta Subsidiary, to request an Advance from the Lenders up to a certain amount to the extent that the Company may request an Advance in such amount and to increase the amount of Cash that the Malta Subsidiary may hold outside of the United States, as set forth in greater detail in the Fifth Amendment.

May 2023 Fourth Amendment to the Loan and Security Agreement

On May 8, 2023, we entered into the Waiver and Fourth Amendment to the Loan Agreement, or the Fourth Amendment, with Hercules, in its capacity as administrative agent and collateral agent, and the Lenders. The Fourth Amendment increased the amount of Cash that could be held by the Malta Subsidiary outside of the United States from $3.0 million to $15.0 million for a 45-day period after the closing of the Fourth Amendment and to $10.0 million thereafter. The Fourth Amendment also waived any purported default with respect to the amount of cash held by the Malta Subsidiary prior to the date of the Fourth Amendment. In August 2023, Hercules granted Axsome a waiver to the Fourth Amendment, permitting the Malta Subsidiary to hold up to $12.5 million in Cash outside of the United States until December 31, 2023.

January 2023 Third Amendment to the Loan and Security Agreement

On January 9, 2023, we entered into the Third Amendment.

The Third Amendment amended the terms of the Loan Agreement to, among other things:

- Extend the maturity date to January 1, 2028, unless the Company meets certain revenue targets as described in the Loan Agreement, in which case the Company can extend the maturity date to January 1, 2029;
- Increase the aggregate principal amount under the Loan Agreement from $300.0 million to $350.0 million;
- Subject to the terms and conditions in the Loan Agreement, change the term loan advance amounts and availability dates under the Tranche 1 Advance through Tranche 5 Advance, including increasing the Tranche 1 Advance from one tranche of $95.0 million to five sub-tranches of $95.0 million, $55.0 million, $30.0 million, $35.0 million, and $35.0 million, respectively, changing the Tranche 2 Advance from three sub-tranches of $35.0 million, $35.0 million, and $30.0 million, respectively, to one tranche of $25.0 million, changing the Tranche 3 Advance from two sub-tranches of $15.0 million and $5.0 million, respectively, to one tranche of $75.0 million, and removing the Tranche 4 Advance and Tranche 5 Advance entirely;
- Revise the interest rate applicable to extensions of credit under the Loan Agreement to equal (a) if the prime rate is greater than or equal to 7.00%, the greater of either (i) the prime rate plus 2.20%, and (ii) 9.95%, but in no event greater than 10.70%, and (b) if the prime rate is less than 7.00%, 9.70%;
- Increase the minimum cash requirement of the Company to the sum of $30.0 million plus the Qualified Cash A/P Amount; and
- Require the Company to pay a facility fee equal to 0.75% of the amount of principal actually funded pursuant to the Tranche 1B Advance, Tranche 1C Advance, Tranche 1D Advance, Tranche 1E Advance, Tranche 2 Advance, and Tranche 3 Advance.

We allowed Tranche 2, which totaled $25.0 million, to expire undrawn.

Royalty Agreements

Pursuant to the Asset Purchase Agreement, dated as of March 25, 2022, or the Purchase Agreement, we agreed to make non-refundable, non-creditable royalty payments to Jazz equal to a (A) high-single digit royalty for any Current Indication or (B) mid-single digit royalty for any Future Indication, of Net Sales in the U.S. Territory made during the applicable Royalty Term (in each case, as those terms are defined in the Purchase Agreement). There are no royalty payments due to Jazz for Net Sales outside of the U.S. Territory.

At the initial closing, we assumed all of the commitments of Jazz to SK and Aerial. SK is the originator of Sunosi and retains rights in 12 Asian markets, including China, Korea, and Japan. In 2014, Jazz acquired from Aerial worldwide rights to Sunosi excluding those Asian markets stated previously. The assumed commitments to SK and Aerial include single-digit tiered royalties based on our sales of Sunosi, and we are committed to pay up to $165.0 million based on revenue milestones and $1.0 million based on development milestones.

Shelf Registration Statement

On December 2, 2022, we filed the 2022 Shelf Registration Statement on Form S-3ASR (File No. 333-235372) with the SEC for the issuance of common stock, preferred stock, warrants, rights, debt securities, and units, which became effective immediately upon filing. At the time any of the securities covered by the 2022 Shelf Registration Statement are offered for sale, we prepare and file a prospectus supplement with the SEC containing specific information about the terms of any such offering.

Off-Balance Sheet Arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined by applicable SEC regulations.

Recent Accounting Pronouncements

Refer to Note 2. Summary of Significant Accounting Policies to our consolidated financial statements included in Part IV, Exhibits and Financial Statement Schedules, of this Annual Report on Form 10-K for a discussion of recently issued accounting pronouncements.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURE ABOUT MARKET RISK

Interest Rate Risk

We are exposed to market risks in the ordinary course of our business. These market risks are principally limited to interest rate fluctuations. We had cash of $315.4 million as of December 31, 2024. The primary objective of our investment activities is to preserve principal and liquidity while maximizing income without significantly increasing risk. We do not enter into investments for trading or speculative purposes. Due to the short-term nature of our investment portfolio and debt agreement, which use short-term interest rates and the prime rate, respectively, we do not believe an immediate 100 basis point increase in interest rates would have a material effect on the fair market value of our portfolio, and, accordingly, we do not expect our operating results or cash flows to be materially affected by a sudden change in market interest rates.

Foreign Currency Exchange Risk

We contract with vendors and third-party manufactures located in Europe and certain invoices are denominated in foreign currencies. Royalty revenues from Pharmanovia are derived from their sales of Sunosi in ex-U.S markets and those sales are denominated in Euros. We are therefore subject to fluctuations in foreign currency rates for the Euro, Swiss Franc, and British Pound, in connection with these agreements, and recognize foreign exchange gains or losses in our statement of operations. We have not historically hedged our foreign currency exchange rate risk. To date, we have not incurred any material effects from foreign currency changes on these transactions.

We do not believe a 10% change in these currencies on December 31, 2024 would have had a material effect on our results of operations or financial condition.

Inflation Risk

Inflation generally affects us by increasing our cost of labor and pricing of contracts. We do not believe that inflation has had a material effect on our business, financial condition, or results of operations during the year ended December 31, 2024.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA.

Our consolidated financial statements and the notes thereto, included in Part IV, Item 15(a), part 1, are incorporated by reference into this Item 8.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE.

None.

ITEM 9A. CONTROLS AND PROCEDURES.

Evaluation of Disclosure Controls and Procedures. Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2024. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, mean controls and other procedures of a company that are designed to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to management, including our principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2024, our principal executive officer and principal financial officer concluded that, as of such date, our disclosure controls and procedures were effective.

Management's Annual Report on Internal Controls over Financial Reporting. Our management is responsible for establishing and maintaining adequate internal controls 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 controls over financial reporting as of December 31, 2024. In making this assessment, our management used the criteria established in Internal Control – Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission, or COSO Framework. Our management has concluded that, as of December 31, 2024, our internal control over financial reporting was effective based on these criteria.

The independent registered public accounting firm, Deloitte & Touche LLP, has issued an attestation report on our internal control over financial reporting. The report on the audit of internal control over financial reporting is included in this Annual Report on Form 10-K.

Inherent Limitations on Effectiveness of Controls. Our management, including our principal executive officer and principal financial officer, does not expect that our internal controls over financial reporting and procedures will prevent all errors and 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.

Changes in Internal Controls over Financial Reporting. There has been no change in our internal controls over financial reporting (as defined in Rule 13a-15(f) of the Exchange Act) that occurred during the period covered by this report, that materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION.

During the fourth quarter of 2024, the Company's directors or officers did not adopt or terminate any Rule 10b5-1 trading arrangements (as defined in Item 408(a)(1)(i) of Regulation S-K) or non-Rule 10b5-1 trading arrangements (as defined in Item 408(c) of Regulation S-K) intended to satisfy the affirmative defense of Rule 10b5-1(c) of the Exchange Act.

During the fourth quarter of 2024, the Company did not adopt or terminate a Rule 10b5-1 trading arrangement (as defined in Item 408(a)(1)(i) of Regulation S-K) for the purchase or sale of securities of the Company, whether or not intended to satisfy the affirmative defense conditions of Rule 10b5-1(c) of the Exchange Act.

ITEM 9C. DISCLOSURE REGARDING FOREIGN JURISDICTIONS THAT PREVENT INSPECTIONS

None.

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 2025 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

ITEM 11. EXECUTIVE COMPENSATION.

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2025 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

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 2025 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

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 2025 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES.

The information required by this Item is incorporated herein by reference from our Proxy Statement for our 2025 Annual Meeting of Stockholders or will be included in an amendment to this Annual Report on Form 10-K.

PART IV

ITEM 15. EXHIBITS and FINANCIAL STATEMENT SCHEDULES.

(a) 1. Consolidated Financial Statements

The following consolidated financial statements of Axsome Therapeutics, Inc. are filed as part of this report.

Contents	Page
Reports of Independent Registered Public Accounting Firm (PCAOB ID: 34) (PCAOB ID: 42)	F-1
Consolidated Balance Sheets as of December 31, 2024 and 2023	F-5
Consolidated Statements of Operations for the Years Ended December 31, 2024, 2023, and 2022	F-6
Consolidated Statements of Stockholders' Equity for the Years Ended December 31, 2024, 2023, and 2022	F-7
Consolidated Statements of Cash Flows for the Years Ended December 31, 2024, 2023, and 2022	F-8
Notes to the Consolidated Financial Statements	F-9

2. Consolidated Financial Statement Schedules

The financial statement schedule entitled "Schedule II – Valuation and Qualifying Accounts" has been omitted since the information required is included in the consolidated financial statements and notes thereto. Other schedules are omitted because they are not applicable, or the required information is shown in the Financial Statements or notes thereto.

3. Exhibits

The list of exhibits filed with this report is set forth in the Exhibit Index following the signature page and is incorporated herein by reference.

Axsome Therapeutics, Inc.
Index to Consolidated Financial Statements

	Page
Reports of Independent Registered Public Accounting Firm	F-1
Consolidated Balance Sheets as of December 31, 2024 and 2023	F-5
Consolidated Statements of Operations for the years ended December 31, 2024, 2023, and 2022	F-6
Consolidated Statements of Stockholders' Equity for the years ended December 31, 2024, 2023, and 2022	F-7
Consolidated Statements of Cash Flows for the years ended December 31, 2024, 2023, and 2022	F-8
Notes to Consolidated Financial Statements	F-9

Report of Independent Registered Public Accounting Firm

To the shareholders and the Board of Directors of Axsome Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Axsome Therapeutics, Inc. and subsidiaries (the "Company") as of December 31, 2024 and 2023, the related consolidated statements of operations, stockholders' equity, and cash flows for each of the two years in the period ended December 31, 2024, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2024 and 2023, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2024, in conformity with accounting principles generally accepted in the United States of America.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2024, based on criteria established in *Internal Control — Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated February 18, 2025, expressed an unqualified opinion on the Company's internal control over financial reporting.

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 audits. We are a public accounting firm registered with the 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 audits 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. Our audits 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 audits 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 audits provide 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 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 financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the 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.

Reserves for Variable Consideration - Commercial Managed Care — *Refer to Note 2 to the financial statements*

Critical Audit Matter Description

As more fully disclosed in Note 2 to the financial statements, the Company records revenues net of provisions for rebates, discounts, and other incentives and returns, which are established at the time of sale. These reductions are attributed to various commercial arrangements, managed healthcare organizations, and government programs that mandate various reductions from list price.

Chargebacks and cash discounts are reflected as a reduction to receivables and settled through the issuance of credits to the customer. All other rebates, discounts and adjustments, are reflected as a liability and settled through cash payments.

The provision related to Commercial Managed Care rebate programs (the "Commercial rebate accruals") involves the use of significant assumptions and judgments in its calculation. These significant assumptions and judgments include consideration of prior payment history, customer utilization mix data, changes to product price, expected patient usage, claims timing lags, and inventory levels in the distribution channel.

Given the complexity involved in determining the assumptions used in calculating the Commercial rebate accruals, auditing these estimates involved especially subjective judgment.

How the Critical Audit Matter Was Addressed in the Audit

Our audit procedures related to Commercial rebate accruals included the following, among others:

- We evaluated the appropriateness and consistency of the Company's methods and assumptions used to calculate Commercial rebate accruals.
- We tested the effectiveness of internal controls over the review of the Company's estimation model, including underlying assumptions and key inputs into the Company's process to calculate Commercial rebate accruals.
- We tested the mathematical accuracy of Commercial rebate accruals.
- We tested the assumptions and key inputs used to calculate Commercial rebate accruals.
- We evaluated the Company's ability to estimate Commercial rebate accruals accurately by comparing actual amounts incurred for Commercial rebate accruals.
- We tested the overall reasonableness of the Commercial rebate accruals recorded at period end by developing an expectation for comparison to actual recorded balances.
- We involved audit professionals with industry and quantitative analytics experience to assist us in performing our auditing procedures.

/s/ Deloitte & Touche LLP

Morristown, New Jersey

February 18, 2025

We have served as the Company's auditor since 2023.

Report of Independent Registered Public Accounting Firm

To the shareholders and the Board of Directors of Axsome Therapeutics, Inc.

Opinion on Internal Control over Financial Reporting

We have audited the internal control over financial reporting of Axsome Therapeutics, Inc. and subsidiaries (the "Company") as of December 31, 2024, based on criteria established in *Internal Control — Integrated Framework (2013)* issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). In our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2024, based on criteria established in *Internal Control — Integrated Framework (2013)* issued by COSO.

We have also audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated financial statements as of and for the year ended December 31, 2024, of the Company and our report dated February 18, 2025, expressed an unqualified opinion on those financial statements.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting, included in the accompanying Management's Annual Report on Internal Controls over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the 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 effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control over Financial Reporting

A company's internal control over financial reporting is a process designed 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. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Deloitte & Touche LLP

Morristown, New Jersey

February 18, 2025

Report of Independent Registered Public Accounting Firm

To the Shareholders and the Board of Directors of Axsome Therapeutics, Inc.

Opinion on the Financial Statements

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

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 audits. 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 audits 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. Our audits 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 audits 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 audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor from 2014 to 2023.

New York, New York

February 27, 2023

Axsome Therapeutics, Inc.
Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	December 31, 2024	December 31, 2023
Assets		
Current assets:		
Cash and cash equivalents	$ 315,353	$ 386,193
Accounts receivable, net	142,001	94,820
Inventories, net	15,732	15,135
Prepaid and other current assets	11,978	8,115
Total current assets	485,064	504,263
Equipment, net	584	846
Right-of-use asset - operating lease	5,383	6,772
Goodwill	12,042	12,042
Intangible asset, net	46,894	53,286
Non-current inventory and other assets	18,531	11,027
Total assets	$ 568,498	$ 588,236
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 71,997	$ 40,679
Accrued expenses and other current liabilities	147,987	90,501
Operating lease liability, current portion	1,835	1,267
Contingent consideration, current	8,285	6,407
Total current liabilities	230,104	138,854
Contingent consideration, non-current	91,680	73,300
Loan payable, long-term	180,710	178,070
Operating lease liability, long-term	6,046	7,035
Finance lease liability, long-term	2,943	—
Total liabilities	511,483	397,259
Stockholders' equity:		
Preferred stock, $0.0001 par value per share (10,000,000 shares authorized, none issued and outstanding)	—	—
Common stock, $0.0001 par value per share (150,000,000 shares authorized, 48,667,587 and 47,351,363 shares issued and outstanding at December 31, 2024 and December 31, 2023, respectively)	5	5
Additional paid-in capital	1,179,797	1,026,543
Accumulated deficit	(1,122,787)	(835,571)
Total stockholders' equity	57,015	190,977
Total liabilities and stockholders' equity	$ 568,498	$ 588,236

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

Axsome Therapeutics, Inc.
Consolidated Statements of Operations
(In thousands, except share and per share amounts)

	Year ended December 31,		
	2024	2023	2022
Revenues:			
Product sales, net	$ 381,677	$ 202,460	$ 50,037
License revenue	—	65,735	—
Royalty and milestone revenue	4,016	2,405	—
Total revenues	385,693	270,600	50,037
Operating expenses:			
Cost of revenue (excluding amortization and depreciation)	33,303	26,065	5,198
Research and development	187,077	97,944	57,947
Selling, general and administrative	411,359	323,123	159,254
Loss in fair value of contingent consideration	28,124	48,918	3,298
Intangible asset amortization	6,392	6,375	4,139
Total operating expenses	666,255	502,425	229,836
Loss from operations	(280,562)	(231,825)	(179,799)
Interest expense, net	(6,569)	(6,453)	(7,335)
Loss before income taxes	(287,131)	(238,278)	(187,134)
Income tax expense	(85)	(960)	—
Net loss	$ (287,216)	$ (239,238)	$ (187,134)
Net loss per common share, basic and diluted	$ (5.99)	$ (5.27)	$ (4.60)
Weighted average common shares outstanding, basic and diluted	47,914,253	45,425,212	40,655,941

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

Axsome Therapeutics, Inc.
Consolidated Statements of Stockholders' Equity
(In thousands, except share amounts)

	Common stock		Additional paid-in capital	Accumulated deficit	Total stockholders' equity
	Shares	Amount			
Balance at December 31, 2021	37,816,794	4	424,826	(409,199)	15,631
Stock-based compensation	—	—	37,726	—	37,726
Issuance of common stock upon exercise of options	340,149	—	6,251	—	6,251
Issuance of common stock upon vesting of RSUs	21,214	—	—	—	
Issuance of common stock upon financing	5,320,460	—	236,788	—	236,788
Issuance of warrants	—	—	826	—	826
Shares tendered for withholding taxes	—	—	(532)	—	(532)
Net loss	—	—	—	(187,134)	(187,134)
Balance at December 31, 2022	43,498,617	4	705,885	(596,333)	109,556
Stock-based compensation	—	—	65,357	—	65,357
Issuance of common stock upon exercise of options	358,760	—	12,419	—	12,419
Issuance of common stock upon vesting of RSUs	43,986	—	—	—	
Issuance of common stock upon financing	3,450,000	1	243,082	—	243,083
Issuance of warrants	—	—	1,635	—	1,635
Shares tendered for withholding taxes	—	—	(1,835)	—	(1,835)
Net loss	—	—	—	(239,238)	(239,238)
Balance at December 31, 2023	47,351,363	5	1,026,543	(835,571)	190,977
Stock-based compensation	—	—	86,558	—	86,558
Issuance of common stock upon exercise of options and under employee stock purchase plan	770,531	—	30,680	—	30,680
Issuance of common stock upon vesting of RSUs	79,585	—	—	—	
Issuance of common stock upon financing	466,108	—	39,968	—	39,968
Shares tendered for withholding taxes	—	—	(3,952)	—	(3,952)
Net loss	—	—	—	(287,216)	(287,216)
Balance at December 31, 2024	48,667,587	5	1,179,797	(1,122,787)	57,015

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

Axsome Therapeutics, Inc.
Consolidated Statements of Cash Flows
(In thousands)

	Year ended December 31,		
	2024	2023	2022
Cash flows from operating activities			
Net loss	$ (287,216)	$ (239,238)	$ (187,134)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	85,218	62,620	37,726
Amortization of intangible asset	6,392	6,375	4,139
Amortization of debt discount	2,640	2,574	1,483
Depreciation	532	459	263
Loss in fair value of contingent consideration	28,124	48,918	3,298
Non-cash lease expense	1,388	1,450	1,162
Right-of-use asset amortization for finance lease	1,034	—	—
Change in operating lease liability	(422)	154	(1,118)
Changes in operating assets and liabilities:			
Accounts receivable, net	(47,181)	(57,121)	(37,699)
Inventories, net	744	(8,156)	(1,331)
Prepaid expenses and other current assets	(3,863)	(5,335)	(2,735)
Non-current inventory and other assets	(3,183)	3,694	(3,944)
Accounts payable	31,318	2,074	25,456
Accrued expenses and other current liabilities	56,065	36,452	43,923
Net cash used in operating activities	(128,410)	(145,080)	(116,511)
Cash flows from investing activities			
Purchases of equipment	(270)	(582)	(702)
Cash paid for business combination	—	—	(53,000)
Net cash used in investing activities	(270)	(582)	(53,702)
Cash flows from financing activities			
Proceeds from draw down of debt	—	85,000	45,000
Payment of debt issuance costs	—	(1,442)	(487)
Payments on principal portion of finance lease obligation	(990)	—	—
Proceeds from issuance of common stock upon financing	40,784	258,750	243,763
Cash paid for common stock issuance costs	(816)	(15,668)	(6,975)
Proceeds from issuance of common stock upon exercise of options and under employee stock purchase plan	30,680	12,419	6,251
Payment of contingent consideration	(7,866)	(6,211)	(2,438)
Payments of tax withholdings on stock awards	(3,952)	(1,835)	(532)
Net cash provided by financing activities	57,840	331,013	284,582
Net (decrease) increase in cash	(70,840)	185,351	114,369
Cash at beginning of period	386,193	200,842	86,473
Cash at end of period	$ 315,353	$ 386,193	$ 200,842
Supplemental disclosures of cash flow information:			
Interest paid	$ 19,690	$ 16,730	$ 7,686
Operating lease right-of-use asset obtained in exchange for operating lease liability	—	7,802	$ 561
Finance lease right-of-use asset obtained in exchange for finance lease liability	5,355	—	—
Supplemental disclosures of non-cash investing activity:			
Fair value of contingent consideration in a business combination	99,965	79,707	37,000
Supplemental disclosures of non-cash financing activity:			
Issuance of warrants in connection with debt financing	—	1,635	—

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

Axsome Therapeutics, Inc.
Notes to Consolidated Financial Statements
(In thousands, except share and per share amounts)

Note 1. Nature of Business and Basis of Presentation

Axsome Therapeutics, Inc. ("Axsome" or the "Company") is a biopharmaceutical company leading a new era in the treatment of central nervous system ("CNS") disorders. The Company delivers scientific breakthroughs by identifying critical gaps in care and develops differentiated products with a focus on novel mechanisms of action that enable meaningful advancements in patient outcomes. Axsome was incorporated on January 12, 2012, in the State of Delaware. The Company's CNS portfolio includes three approved products – Auvelity® (the components of which are referred to as "AXS-05"), Sunosi® (the components of which are referred to as "solriamfetol"), both of which are also being developed for further indications, and Symbravo® (the components of which are referred to as "AXS-07"), which was recently approved by the FDA on January 30, 2025 – as well as two product candidates, AXS-12, and AXS-14, which are being developed for multiple indications. The Company refers herein to Auvelity, Sunosi, Symbravo, AXS-12, AXS-14, and its programs to develop additional indications for AXS-05 and solriamfetol as the Company's products.

The Company acquired the U.S. rights to Sunosi from Jazz Pharmaceuticals plc ("Jazz") in May 2022 and worldwide ex-U.S. rights (excluding certain Asian markets) from Jazz in November 2022 (collectively, the "Acquisition"). Sunosi is a product approved by the U.S. Food and Drug Administration (the "FDA") and marketed in the U.S. to improve wakefulness in adult patients with excessive daytime sleepiness ("EDS") associated with narcolepsy or obstructive sleep apnea. Sunosi was approved in Europe in January 2020 by the European Commission. In February 2023, the Company announced a licensing transaction with Atnahs Pharma UK Limited ("Pharmanovia") to market Sunosi in Europe and certain countries in the Middle East / North Africa.

The Company announced, in August 2022, FDA approval of Auvelity, and in October 2022, the U.S. commercial availability of Auvelity, for the treatment of major depressive disorder in adults.

The Company announced, in January 2025, FDA approval of Symbravo (meloxicam and rizatriptan) for the acute treatment of migraine with or without aura in adults.

The accompanying consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States of America ("GAAP"). The consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All material intercompany accounts and transactions have been eliminated during the consolidation process.

Liquidity and Capital Resources

The Company has incurred operating losses since its inception and expects to continue to incur operating losses and may never become profitable. As of December 31, 2024, the Company had an accumulated deficit of $1,122.8 million.

The Company's primary sources of cash have been proceeds from the sales of Auvelity and Sunosi, the issuance and sale of its common stock in public offerings, and the issuance of debt. The Company's ability to achieve profitability depends on a number of factors, including its ability to obtain regulatory approval for its product candidates, successfully complete any post-approval regulatory obligations and successfully commercialize its product candidates alone or in partnership with third parties. The Company may continue to incur substantial operating losses even as it continues to generate revenues from its products.

The Company believes its existing cash will be sufficient to fund its anticipated operating cash requirements for at least twelve months following the date of this filing. During that time, the Company expects that its expenses will increase primarily due to the commercialization of Auvelity, Sunosi, and Symbravo while continuing to further develop the Company's pipeline assets. The Company may use a combination of public and private equity offerings, debt financings, other third-party funding, strategic alliances, licensing arrangements or marketing and distribution arrangements if market conditions are favorable or as a result of other strategic considerations to finance its future cash needs.

The Company's common stock is listed on The Nasdaq Global Market and trades under the symbol "AXSM."

Note 2. Summary of Significant Accounting Policies

Significant Risks and Uncertainties

The Company's operations are subject to a number of factors that can affect its operating results and financial condition. Such factors include, but are not limited to: the results of clinical testing and trial activities of the Company's product candidates; the Company's ability to obtain regulatory approval to market its products; competition from products manufactured and sold or being developed by other companies; the price of, and demand for, the Company's products; the Company's ability to negotiate favorable licensing or other manufacturing and marketing agreements for its products; and the Company's ability to raise additional capital. If the Company's commercialization of its products is not financially successful, it will be unable to generate sufficient recurring product revenue to achieve and maintain profitability.

The Company currently has three commercial products, Auvelity and Sunosi, and recently FDA-approved product, Symbravo, and there can be no assurance that the Company's research and development efforts will result in successfully commercialized products in addition to Auvelity and Sunosi. Developing and commercializing a product requires significant time and capital and is subject to regulatory review and approval as well as competition from other biotechnology and pharmaceutical companies. The Company operates in an environment of rapid change and is dependent upon the continued services of its employees and consultants and obtaining and protecting intellectual property.

Use of Estimates

Management considers many factors in developing the estimates and assumptions that are used in the preparation of these financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, including expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates, and whether historical trends are expected to be representative of future trends. The estimation process often may yield a range of potentially reasonable estimates of ultimate future outcomes, and management must select an amount that falls within that range of reasonable estimates. This process may result in actual results differing materially from those estimated amounts used in the preparation of the financial statements if these results differ from historical experience, or other assumptions do not turn out to be substantially accurate, even if such assumptions are reasonable when made. In preparing these financial statements, management used significant estimates in the following areas, among others: stock-based compensation expense; determination of fair value of warrants; accounting for research and development costs; accounting for acquisitions; impairments of goodwill and the intangible asset; determination of fair value of contingent consideration; chargebacks, cash discounts, sales rebates, returns and other adjustments; and the recoverability of the Company's net deferred tax assets and related valuation allowance.

Revenue Recognition

In accordance with Accounting Standards Codification ("ASC") Topic 606, Revenue from Contracts with Customers ("ASC 606") the Company recognizes revenue when the customer obtains control of a promised good or service, in an amount that reflects the consideration that the Company expects to receive in exchange for the good or service. Transfer of control is based on contractual performance obligations, which occurs upon transfer of the title along with the physical transfer of the Company's goods to the customer, as that is when the customer has obtained control of significantly all of the economic benefits and the Company obtains a right of payment.

To determine revenue recognition for arrangements that the Company determines are within the scope of ASC 606, the Company performs the following five steps: (i) identify the contract(s) with a customer, (ii) identify the performance obligations in the contract, (iii) determine the transaction price, (iv) allocate the transaction price to the performance obligations in the contract, and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step model to arrangements that meet the definition of a contract under ASC 606, including when it is probable that the Company will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract and determines those that are performance obligations and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied. For a complete discussion of accounting for product sales, see Product Sales, net (below) and Note 15. Revenues.

License Agreements

The Company generates revenue from license or similar agreements with pharmaceutical companies for the development and commercialization of certain products. Such agreements may include the transfer of intellectual property rights in the form of licenses. Payments made by the customer may include non-refundable upfront fees, payments based upon the achievement of defined milestones, and royalties on sales of products.

If a license to the Company's intellectual property is determined to be distinct from the other performance obligations identified in the arrangement, the Company recognizes the transaction price allocated to the license as revenue upon transfer of control of the license. All other promised goods or services in the agreement are evaluated to determine if they are distinct. If they are not distinct, they are combined with other promised goods or services to create a bundle of promised goods or services that is distinct. Optional future services where any additional consideration paid to the Company reflects their standalone selling prices do not provide the customer with a material right, and, therefore, are not considered performance obligations. If optional future services are priced in a manner which provides the customer with a significant or incremental discount, they are material rights and are accounted for as separate performance obligations.

Contingent milestones at contract inception are estimated to the extent that it is probable that a significant revenue reversal would not occur and are included in the transaction price using the most likely amount method. Milestone payments that are not within the Company's control, such as regulatory approvals, are not considered probable of being achieved until those approvals are received, and, therefore, the variable consideration is constrained. The transaction price is then allocated to each performance obligation on a relative stand-alone selling price basis, for which the Company recognizes revenue as or when the performance obligations under the contract are satisfied. At the end of each reporting period, the Company re-evaluates the probability of achieving development or sales-based milestone payments that a significant revenue reversal would not occur and, if necessary, adjusts the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect license and other revenue, as well as earnings, in the period of adjustment.

For arrangements that include sales-based royalties, including sales-based milestone payments, and a license of intellectual property that is deemed to be the predominant item to which the royalties relate, revenue is recognized at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalties have been allocated has been satisfied (or partially satisfied).

Product Sales, net

Revenues from product sales are recorded net of reserves for variable consideration. These reserves reflect the Company's best estimate of the amount of consideration to which the Company is entitled based on the terms of the contracts. The Company sells Auvelity and Sunosi in the United States to wholesale distributors with whom the Company has entered into formal agreements (collectively, the "Distributors"). These Distributors subsequently resell the Company's products to retail pharmacies. The Company also sells Sunosi to Distributors in Canada and on a product supply basis to Pharmanovia. Sunosi is subsequently sold by Pharmanovia in certain ex-U.S. markets. The Company does not sell products under consignment arrangements, and the collection of proceeds from product sales is not contingent upon customers' sale of the goods to third parties. The Company received FDA approval for Symbravo in January 2025 and did not record any product sales with respect to Symbravo for the periods covered by this report. See Note 15. Revenues for a further breakout of product sales, net.

Reserves for Variable Consideration

The Company's estimates of variable consideration and determination of whether to include estimated amounts in the transaction price are based largely on an assessment of its anticipated performance and all information (historical, current and forecasted) that is reasonably available. These reserves reflect the Company's best estimate of the amount of consideration to which the Company is entitled based on the terms of the contracts and are classified as reductions to accounts receivable, net if payable to a customer or accrued expenses and other current liabilities if payable to a third-party. The amount of variable consideration that is included in the transaction price may be constrained and is included in the net sales price only to the extent that is considered probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration ultimately received may differ from the estimates. If actual results in the future vary from our estimates, the Company will adjust these estimates, which would affect net product revenue and earnings in the period such variances become known.

The provision for rebates, discounts, and other incentives is based on expected patient usage, as well as inventory levels in the distribution channel to determine the contractual obligation to the benefit providers. Additionally, sales are generally made with a limited right of return under certain conditions. Revenues are recorded net of provisions for rebates, discounts, and other incentives and returns, which are established at the time of sale. The Company uses customer segment utilization mix data, changes to product price, government pricing calculations and prior payment history in order to estimate the variable consideration. Amounts accrued for rebates, discounts, and other incentives are adjusted when trends indicate that adjustment is appropriate and to reflect actual experience.

Trade Discounts and Allowances - The Company generally provides discounts which include incentive fees that are explicitly stated in the Company's contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized. In addition, the Company compensates (through trade discounts and allowances) its distributors for distribution services and data. These payments have been recorded as a reduction to product sales as well as a reduction to accounts receivable, net on the consolidated balance sheets.

Product Returns - The Company generally offers a limited right of return for product that has been purchased from the Company based on the product's expiration date. The Company estimates the amount of its product sales that may be returned and records this estimate as a reduction of revenue in the period the related product sale is recognized, as well as a component of accrued expense and other current liabilities. The Company currently estimates product return liabilities using available industry data, historical product sales information, and actual returns experience.

Chargebacks and Discounts - Chargebacks for fees and discounts to providers represent the estimated obligations resulting from contractual commitments to sell products at prices lower than the list prices charged to distributors. Distributors charge the Company for the difference between what they pay for the product and the ultimate selling price. These reserves are established in the same period that the related product sales are recognized, resulting in a reduction to product sales and accounts receivable, net.

Rebates - Rebates apply to: Medicaid, managed care, and supplemental rebates to all applicable states as defined by the statutory government pricing calculation requirements under the Medicaid Drug Rebate Program. Tricare rebates to the TRICARE third-party administrator are based on the statutory calculation defined in the agreement with the Defense Health Agency. Part D and Commercial Managed Care rebates are paid based on the contracts with Pharmacy Benefit Managers ("PBMs") and Managed Care Organizations. Rebates are paid to these entities upon receipt of an invoice from the contracted entity which is based on the utilization of the product by the members of the contracted entity. Allowances for rebates also include amounts due under the Inflation Reduction Act of 2022 for Medicare Part D. The Company estimates these rebates and records such estimates in the same period the related product sales are recognized, resulting in a reduction to product sales as well as a component of accrued expenses and other current liabilities.

Coverage Gap - The Medicare Part D coverage gap is a period of consumer payment for prescription medication costs which lies between the initial coverage limit and the catastrophic-coverage threshold, when the patient is a member of a Medicare Part D prescription-drug program administered by the Centers for Medicare & Medicaid Services. The Company estimates the percentage of goods sold to patients in the Coverage Gap and adjusts the transaction price for such discount at the time of sale resulting in a reduction to product sales as well as a component of accrued expenses and other current liabilities.

Other Incentives - Other incentives which the Company offers include voluntary patient assistance programs, such as the co-pay assistance program, which are intended to provide financial assistance to qualified commercially-insured patients with prescription drug co-payments required by payers. The calculation of the accrual for co-pay assistance is based on an estimate of claims and the cost per claim that the Company expects to receive associated with product that has been recognized as revenue. The reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product sales as well as a component of accrued expenses and other current liabilities.

The Company makes significant estimates and judgments that materially affect its recognition of net product revenue. Claims by third-party payors for rebates, chargebacks and discounts frequently are submitted to the Company significantly after the related sales, potentially resulting in adjustments in the period in which the new information becomes known. The Company will adjust its estimates based on new information, including information regarding actual rebates, chargebacks and discounts for its products, as it becomes available.

Cost of Revenue

The Company's cost of revenue consists of cost of product sales, fee sharing expense related to the upfront license revenue received, and expense related to a sales-based milestone. Cost of product sales primarily include direct costs (inclusive of material, shipping, handling, and manufacturing costs), overhead and product royalties. Cost of product sales excludes depreciation and amortization. In the fourth quarter of 2024, the Company recorded a $2.5 million expense for the achievement of a sales-based milestone related to world-wide Sunosi sales. In the first quarter of 2023, the Company recorded a $5.0 million fee sharing expense related to the upfront license revenue received.

The Company assumed royalty and sales-based milestone commitments of Jazz to SK Biopharmaceuticals Co. Ltd. ("SK") and Aerial Biopharma, LLC ("Aerial"). SK is the originator of Sunosi and retains rights in 12 Asian markets, including China, Korea and Japan. In 2014, Jazz acquired from Aerial worldwide rights to Sunosi excluding those Asian markets stated previously. The assumed commitments to SK and Aerial include single-digit tiered royalties based on the Company's sales of Sunosi, and the Company is committed to pay up to $165 million based on revenue milestones and $1 million based on development milestones. Additionally, the Company pays a royalty to Antecip Bioventures II LLC ("Antecip"), an entity owned by Axsome's Chief Executive Officer and Chairman of the Board of Directors (the "Board"), Herriot Tabuteau, M.D., equal to 3.0% of Auvelity net sales.

Foreign Currency Translation

Revenues and expenses denominated in foreign currency are translated into U.S. dollars at the exchange rate on the date they are incurred. Assets and liabilities of foreign operations are translated at period-end exchange rates. The effect of exchange rate fluctuations on translating foreign currency into U.S. dollars is included in the statements of operations and is not material to the Company's consolidated financial statements.

Segment Information

Operating segments are defined as components of an enterprise for which separate discrete information is available for evaluation by the chief operating decision maker or decision-making group in deciding how to allocate resources and in assessing performance. The Company views its operations and manages its business as one operating and reporting segment, which is the business of developing and delivering novel therapies for the management of CNS disorders. See Note 20. Segment Information for further information.

Cash and Cash Equivalents

The Company considers all highly liquid investments that have maturities of three months or less when acquired to be cash equivalents. The Company's cash and cash equivalents includes holdings in checking and overnight sweep accounts. The Company's cash equivalents, which are money market funds held in a sweep account, are measured at fair value on a recurring basis. As of December 31, 2024, the balance of cash and cash equivalents was $315.4 million, which approximates fair value and was determined based upon Level 1 inputs. The sweep account is valued using quoted market prices with no valuation adjustments applied. Accordingly, these securities are categorized as Level 1 on the fair value hierarchy.

Concentration of Risk

Concentration of Credit Risk - Financial instruments that potentially subject the Company to a concentration of credit risk consist of cash and cash equivalents. The Company maintains its cash deposits at financial institutions, which cash deposits exceed insured limits. At December 31, 2024, the majority of the Company's cash was held by two financial institutions, and amounts on deposit were in excess of government-provided insurance limits. The Company places its cash and cash equivalents in what it believes to be high credit quality banks and money market funds and has not recognized any losses from credit risks on such accounts since inception. See Accounts Receivable, net below for further information.

Concentration of Risk, Other - The Company has a limited number of contract manufacturers for its products. At times, the Company may have only one manufacturer or supplier for its products.

Business Combination

The Company accounted for the Acquisition as a business combination using the acquisition method of accounting, which requires that all identifiable assets acquired, and liabilities assumed be recorded at their estimated fair values. The excess of the fair value of purchase consideration over the fair values of identifiable assets and liabilities is recorded as goodwill. When determining the fair values of assets acquired and liabilities assumed, management makes significant estimates and assumptions. Critical estimates in valuing the intangible asset include but are not limited to future expected cash flows from acquired patented technology. Management's estimates of fair value are based upon assumptions believed to be reasonable, but are inherently uncertain and unpredictable and, as a result, actual results may differ from estimates.

As a result of the Acquisition, the Company recorded goodwill and an intangible asset.

Goodwill

Goodwill is deemed to have an indefinite life and therefore not amortized. The Company tests the carrying amounts of goodwill for recoverability on an annual basis or more frequently if events or changes in circumstances indicate that the asset might be impaired. When reviewing goodwill for impairment, the Company first evaluates the qualitative factors to determine whether it is more likely than not that the fair value of a reporting unit is less than its carrying amount. If the qualitative factors determine it is necessary to complete a goodwill impairment test, the fair value of the relevant reporting unit is determined and compared to its carrying value. If the fair value is greater than the carrying value, then the carrying value is deemed to be recoverable, and no further action is required. If the fair value estimate is less than the carrying value, goodwill is considered impaired for the amount by which the carrying amount exceeds the reporting unit's fair value, and a charge is reported in impairment of goodwill in the Company's consolidated statements of operations. The Company completes its annual goodwill assessment as of December 31. As of December 31, 2024, the Company has determined that it has one reporting unit. The Company has not identified any events or changes in circumstances that indicate the existence of potential impairment of goodwill during the fiscal year ended December 31, 2024. The balance of goodwill was $12.0 million at both December 31, 2024 and December 31, 2023.

Intangible Asset

The Company's intangible asset is amortized using the straight-line method over its estimated period of benefit of ten years. The Company evaluates recoverability of the intangible asset periodically by considering events or changes in circumstances that may warrant revised estimates of useful lives or that indicate the asset may be impaired. The Company has not identified any events or changes in circumstances that indicate the existence of potential impairment of the intangible asset during the year ended December 31, 2024.

Contingent Consideration

Consideration paid in a business combination may include potential future payments that are contingent upon the acquired business achieving certain milestones in the future ("contingent consideration"). The royalty payments due to Jazz are a high single-digit royalty on the Company's U.S. net sales of Sunosi in the current indication and a mid single-digit royalty on the Company's U.S. net sales of Sunosi for future indications. Contingent consideration liabilities are measured at their estimated fair value as of the date of acquisition, with subsequent changes in fair value recorded in the consolidated statements of operations during such period a change is recognized. The Company estimates the fair value of the contingent consideration as of the acquisition date and reporting periods thereafter using the probability weighted income approach and makes significant assumptions, including estimated future sales of Sunosi in current and future indications, timing of regulatory and commercial milestone achievements, probability of technical and regulatory success rates, and discount rates. Contingent consideration liabilities expected to be settled within 12 months after the balance sheet date are presented in current liabilities, with the non-current portion recorded within total liabilities in the consolidated balance sheets.

Fair Value Measurements

Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants at the measurement date. Assets and liabilities that are measured at fair value are reported using a three-level fair value hierarchy that prioritizes the inputs used to measure fair value. This hierarchy maximizes the use of observable inputs and minimizes the use of unobservable inputs. The three levels of inputs used to measure fair value are as follows:

Level 1—Quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Inputs other than quoted prices in active markets that are observable for the asset or liability, either directly or indirectly.

Level 3—Unobservable inputs for which there is little or no market data, which require the reporting entity to develop its own assumptions.

To the extent that valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. An asset's or liability's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The Company's financial instruments are cash and cash equivalents, accounts receivable, accounts payable, accrued expenses and other liabilities, contingent warrant liability, current and long-term debt, and current and non-current contingent consideration. The Company's Level 1 financial instruments include cash and cash equivalents, accounts receivable, accounts payable, and accrued expenses and other liabilities. They are considered Level 1 as the carrying values reported in the accompanying consolidated financial statements approximate their respective fair values due to their short-term maturities. The carrying value of debt on the Company's balance sheet is estimated to approximate its fair value. The Company's Level 3 financial instruments include contingent warrant liability and current and non-current contingent consideration due to the significant unobservable inputs required in determining their respective fair values.

The Company categorized the fair value of contingent consideration liabilities as Level 3 within the fair value hierarchy as the estimate is based on significant unobservable inputs requiring management judgment. The fair value of contingent consideration liabilities is estimated by using the probability weighted income approach using significant assumptions, including estimated future sales of Sunosi in current and future indications, timing of regulatory and commercial milestone achievements, probability of technical and regulatory success and discount rates. Contingent consideration liabilities are subject to remeasurement at each prospective balance sheet date, with any changes in the fair value recorded in the consolidated statements of operations. See Note 8. Fair Value of Financial Instruments for further detail.

The Company estimated the fair value of the warrant liabilities using the Black-Scholes model based on key assumption and inputs. The Company utilizes a probability assessment to estimate the likelihood of vesting for the remaining Loan Agreement (as defined below) warrants and allocated the probability of occurrence percentage to the fair values calculated, and, therefore, is considered Level 3 within the fair value hierarchy. The Company accounts for warrants anticipated to be issued in the future under the Loan Agreement as liabilities and measures them at fair value using the Black-Scholes valuation model. The warrants are subject to remeasurement at each prospective balance sheet date, with any changes in the fair value recorded in the consolidated statements of operations. See Note 8. Fair Value of Financial Instruments for further detail.

Accounts Receivable, net

The Company's accounts receivable, net, arise from product sales and represent amounts due from its customers. They are generally stated at the gross sales amount, less reserves resulting from trade discounts and allowances and chargebacks. Accounts receivable typically have a standard payment term of 60 days or less and do not bear interest.

The Company monitors the financial performance and creditworthiness of its customers so that it can properly assess and respond to changes in the customers' credit profiles. During the first quarter of 2023, the Company began distributing products through wholesale customers. The Company estimates expected credit losses of its accounts receivable by assessing the risk of loss and available relevant information about collectability, including historical credit losses, existing contractual payment terms, actual payment patterns of its customers, individual customer circumstances, and reasonable and supportable forecast of economic conditions expected to exist throughout the contractual life of the receivable. The Company has not historically experienced significant credit losses. Based on its assessment, as of December 31, 2024, the Company has not recorded any allowances for doubtful accounts receivable. For further information about accounts receivable, see Note 4. Accounts Receivable, net.

Debt Issuance Costs

Debt issuance costs consist of costs incurred in obtaining long-term financing. These costs are classified on the consolidated balance sheet as a direct deduction from the carrying amount of the related debt liability and subsequently amortized as interest expense in the consolidated statement of operations using the effective interest rate method.

The Company evaluates amendments to its debt instruments in accordance with ASC 470-50, *Debt – Modifications and Extinguishments* ("ASC 470") to determine whether the amendment should be accounted for as a modification or an extinguishment. An amendment may be considered modified when the terms of the new debt and original instrument are not "substantially different" (as defined in the debt modification guidance in ASC 470). Amendments that are considered modifications are accounted for prospectively as yield adjustments, based on the revised terms, and lender fees and costs directly incurred with third parties, to the extent material, are recorded as debt discount and amortized to interest expense using the effective interest rate method.

Inventory

The Company values its inventories at the lower of cost or estimated net realizable value. The remaining inventory associated with the Acquisition is stated at fair value due to purchase accounting. The Company performs an assessment of the recoverability of capitalized inventory during each reporting period, and it writes down any excess and obsolete inventories to their estimated net realizable value in the period in which the impairment is first identified. Such impairment charges, if they occur, are recorded within cost of revenue.

The Company capitalizes inventory costs associated with the Company's products after regulatory approval when, based on management's judgment, future commercialization is considered probable and the future economic benefit is expected to be realized. Inventory acquired and manufactured prior to receipt of regulatory approval of a product candidate is expensed as research and development expense as incurred. Inventory that can be used in either the production of clinical or commercial product is expensed as research and development expense when selected for use in a clinical manufacturing campaign.

Inventory levels are evaluated for amounts that would be sold within one year. If the level of inventory exceeds the estimated amount that would be sold after the next 12 months, the Company classifies the estimate of such inventory as non-current.

Equipment, net

Equipment consists primarily of computer equipment and is recorded at cost. Equipment is depreciated on a straight-line basis over its estimated useful life, which the Company estimates to be three years. When equipment is sold or otherwise disposed of, the cost and related accumulated depreciation are removed from the accounts and the resulting gain or loss is included in operating expenses.

Research and Development Costs

Research and development costs are expensed as incurred. Research and development expenses consist primarily of employee-related expenses, including salaries, benefits, travel and stock-based compensation expense, contract services, costs incurred to third-party service providers for conducting research, preclinical and clinical studies, laboratory supplies, product license fees, consulting and other related expenses. Research, preclinical and clinical study expenses are estimated based on services performed, pursuant to contracts with third-party research and development organizations that conduct and manage research, preclinical and clinical activities on the Company's behalf, including discussions with internal management personnel and external service providers as to the progress or stage of completion of services and the contracted fees to be paid for such services. If the actual timing of the performance of services or the level of effort varies from the original estimates, accruals are adjusted accordingly. Payments associated with licensing agreements to acquire licenses to develop, use, manufacture and commercialize products that have not reached technological feasibility and do not have alternative future use are expensed as incurred.

Advertising Costs

Advertising costs are included in selling, general and administrative expenses and are expensed as incurred. The Company considers advertising costs as expenses related to the promotion of the Company's commercial products. For the years ended December 31, 2024, 2023, and 2022, advertising costs were $101.2 million, $100.3 million, and $35.3 million, respectively.

Income Taxes

Income taxes are accounted for under the asset and liability method. Under this method, deferred tax assets and liabilities are recognized for the future tax consequences attributable to the differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax bases, operating losses, and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect of a change in tax rates on deferred tax assets and liabilities is recognized in income in the period that includes the enactment date. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company recognizes the tax benefit from an uncertain tax position only if it is more likely than not to be sustained upon examination based on the technical merits of the position as well as consideration of the available facts and circumstances. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. As of December 31, 2024, the Company does not believe any material uncertain tax positions are present. In the event the Company determines that accrual of interest or penalties are necessary in the future, the amount will be presented as a component of income tax expense.

Stock-Based Compensation

For stock options issued, the Company estimates the grant date fair value of each option using the Black-Scholes option pricing model. The Black-Scholes model takes into account the expected volatility of the Company's common stock, the risk-free interest rate, the estimated life of the option, the closing market price of the Company's common stock and the exercise price. The estimates utilized in the Black-Scholes calculation involve inherent uncertainties and the application of management's judgment. In addition, the Company accounts for equity award forfeitures as they occur.

For restricted stock units ("RSUs"), the Company issues them in the form of Company common stock. The fair market value of these awards is based on the market closing price per share on the grant date.

The Company recognizes the grant date fair value of the stock options and RSUs over the requisite service period, which is generally the vesting term. For awards only subject to service-based vesting conditions, the Company elected to recognize stock-based compensation expense on a straight-line basis. For awards subject to performance-based vesting conditions, the Company recognizes stock-based compensation expense using the accelerated attribution method when the achievement of the performance condition becomes probable. The expense related to the stock-based compensation is recorded within the same financial statement line item as the grantee's cash compensation.

The Company's policy upon exercise of stock options and RSUs is that shares will be issued as new shares drawing on the Company's 2015 Omnibus Incentive Compensation Plan share pool that was adopted by the stockholders in November 2015.

Basic and Diluted Net Loss per Common Share

Basic net loss per share of common stock is computed by dividing net loss by the weighted average number of shares of common stock outstanding during the period. Diluted net loss per share of common stock includes the effect, if any, from the potential exercise or conversion of securities, such as warrants, stock options, RSUs and/or common stock pursuant to the 2023 Employee Stock Purchase Plan (the "ESPP"), which would result in the issuance of incremental shares of common stock. As the impact of these items is anti-dilutive during periods of net loss, there was no difference between basic and diluted net loss per share of common stock for the years ended December 31, 2024 and 2023.

Leases

The Company determines if an arrangement is a lease at contract inception. Right-of-use assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. When evaluating whether a contract contains a lease, the Company considers whether (1) the contract explicitly or implicitly identifies assets that are contractually defined and (2) the Company obtains substantially all of the economic benefits from the use of that underlying asset and directs how and for what purpose the asset is used during the term of the contract.

The Company's lease agreements contain lease and non-lease components. Non-lease components primarily include payments for maintenance and utilities. The Company has applied the practical expedient to combine fixed payments for non-lease components with lease payments and account for them together as a single lease component, which increases the amount of lease assets and corresponding liabilities. Payments under the Company's lease arrangements are primarily fixed, however, variable payments are expensed as incurred and not included in the operating lease asset and liability.

Lease assets and liabilities are recognized at the commencement date of the lease based upon the present value of lease payments over the lease term. When determining the lease term, the Company includes options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. The Company uses the interest rate implicit in the contract when such rate is readily determinable and uses the Company's incremental borrowing rate when the rate implicit in the contract is not readily determinable based upon the information available at the commencement date in determining the present value of the lease payments.

The Company's operating leases are reflected in the right-of-use operating asset; operating lease liability, current portion; and operating lease liability, long-term portion in the Company's consolidated balance sheets. Operating lease expense is recognized on a straight-line basis over the lease term and included in selling, general and administrative expenses. Finance leases are included in the non-current inventory and other assets; accrued expenses and other current liabilities; and finance lease liability, long-term in the Company's consolidated balance sheets. Assets under the finance leases are amortized on a straight-line basis over the lease term and included in selling, general and administrative expenses. Short-term leases, defined as leases that have a lease term of 12 months or less at the commencement date, and do not include an option to extend the term or purchase the underlying asset that the Company is reasonably certain to exercise, are excluded from this treatment and are recognized on a straight-line basis over the term of the lease.

Recent Accounting Pronouncements

In October 2021, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2021-08, Business Combinations (Topic 805). This update requires that an entity (acquirer) recognize and measure contract assets and contract liabilities acquired in a business combination in accordance with ASC 606, Revenue from Contracts with Customers. At the acquisition date, an acquirer should account for the related revenue contracts in accordance with ASC 606 as if it had originated the contracts. This differs from the current requirement to measure contract assets and contract liabilities acquired in a business combination at fair value. The amendments in this update should be applied prospectively, and are effective for fiscal years beginning after December 15, 2022, including interim periods within those fiscal years. The Company adopted this standard as of January 1, 2023 and concluded it did not have a material impact on the Company's financial statements. See Note 3. Business Combination for further information.

In November 2023, the FASB issued ASU 2023-07, Segment reporting, which requires disclosure of incremental segment information on an annual and interim basis. The standard is effective for years beginning after December 15, 2023, and interim periods beginning after December 15, 2024, and early adoption is permitted. The Company adopted this standard as of January 1, 2024. See Note 20. Segment Information for further information.

In December 2023, the FASB issued ASU 2023-09, Improvements to Income Tax Disclosures, which requires disclosure of disaggregated income taxes paid by jurisdiction, enhances disclosures in the effective tax rate reconciliation, and modifies other income tax-related disclosures. The amendments are effective for annual periods beginning after December 15, 2024. The Company is currently evaluating the effect of adopting this guidance on its consolidated financial statements.

In November 2024, the FASB issued ASU 2024-03, Income Statement - Reporting Comprehensive Income - Expense Disaggregation Disclosures (Subtopic 220-40): Disaggregation of Income Statement Expenses. This ASU requires additional disaggregated disclosures in the notes to financial statements for certain categories of expenses that are included on the face of the income statement. The guidance is effective for fiscal years beginning after December 15, 2026 and for interim periods within fiscal years beginning after December 15, 2027, with early adoption permitted. The Company is currently evaluating the effect of adopting this guidance on its consolidated financial statements.

Note 3. Business Combination

Acquisition of Assets of Jazz Pharmaceuticals

On March 25, 2022, the Company entered into an Asset Purchase Agreement (the "Purchase Agreement") with Jazz, pursuant to which the Company was to acquire commercial and development rights with respect to Sunosi from Jazz in certain U.S. and ex-U.S. markets. The Acquisition occurred in two separate closings. The sale and purchase of specified initial assets contemplated by the Purchase Agreement occurred on May 9, 2022 (the "Initial Closing"), following the satisfaction or waiver of the closing conditions under the Purchase Agreement. The sale and purchase of specified ex-U.S. assets contemplated by the Purchase Agreement occurred on November 14, 2022, following the satisfaction or waiver of the closing conditions under the Purchase Agreement (the "Final Closing"). The Company accounted for the Initial Closing as a business combination using the acquisition method of accounting, and the Company accounted for the Final Closing as an asset acquisition.

Under the terms of the Purchase Agreement, the Company received from Jazz worldwide commercial, development, manufacturing, and intellectual property rights to Sunosi, except for certain Asian markets. Jazz received from the Company a total upfront payment of $53 million. In addition, Jazz will receive a high single-digit royalty on the Company's U.S. net sales of Sunosi in the current indication, and a mid single-digit royalty on the Company's U.S. net sales of Sunosi in future indications. The Company also assumed the commitments of Jazz to SK and Aerial. SK is the originator of Sunosi and retains rights in 12 Asian markets, including China, Korea and Japan. In 2014, Jazz acquired from Aerial worldwide rights to Sunosi excluding those Asian markets as stated previously. The assumed commitments to SK and Aerial include single-digit tiered royalties based on the Company's sales of Sunosi, and additionally, the Company is committed to pay up to $165 million based on revenue milestones and $1 million based on development milestones. The Company financed the transaction via its existing term loan facility with Hercules Capital, Inc.

The purchase consideration consisted of the following:

Cash at settlement	$	53,000
Fair value of contingent consideration		36,140
Total	$	89,140

The allocation of the fair value of the Acquisition is shown in the table below:

	Amounts recognized as of acquisition date (as previously reported)	Measurement period adjustments [1]	Purchase price allocation
Inventory	$ 10,601	$ —	$ 10,601
Other current assets	3,551	1,587	5,138
Intangible asset	63,800	—	63,800
Goodwill	11,897	145	12,042
Accrued expenses and other current liabilities	(709)	(1,732)	(2,441)
Total	$ 89,140	$ —	$ 89,140

(1) The adjustment to goodwill resulted from rebates and returns during the post-acquisition period, which were provisionally recorded as an asset and liability, respectively, as of the acquisition date.

The net assets were recorded at their estimated fair value. In valuing acquired assets and liabilities, fair value estimates were based primarily on future expected cash flows, market rate assumptions for contractual obligations, and appropriate discount rates.

Inventories acquired included raw materials, work in process and finished goods for Sunosi. Inventories were recorded at their estimated fair values categorized as Level 3. The fair value of finished goods was determined based on the estimated selling price, net of selling costs and a margin on the selling activities. The fair value of work in process was determined based on estimated selling price, net of selling costs and costs to complete the manufacturing, and a margin on the selling and manufacturing activities. The fair value of raw materials was estimated to equal the replacement cost. A step-up in the value of inventory of $1.1 million was originally recorded in connection with the Acquisition and is being amortized through cost of revenue as the underlying product is sold.

Other current assets acquired were sample inventory and the rebates for Sunosi sales by the Company after the Initial Closing to be covered by Jazz.

The intangible asset is acquired developed technology. Fair value was determined by applying the income approach, which recognizes that the fair value of an asset is premised upon the expected receipt of future economic benefits such as earnings and cash inflows based on current sales projections and estimated direct costs, using a discount rate of 43.5% that reflects the return requirements of the market. The intangible asset is being amortized over an estimated useful life of 10 years.

Goodwill is considered an indefinite-lived asset and relates primarily to intangible assets that do not qualify for separate recognition, such as the assembled workforce and synergies between the entities. The Company expects that the entire amount of the purchase price allocated to goodwill will be deductible for U.S. income tax purposes over a 15-year period.

Accrued expenses and other current liabilities acquired were the Company's assumed sales returns liability for Sunosi after the transaction close date related to Sunosi sales recorded by Jazz prior to the Initial Closing.

Pro Forma Consolidated Financial Information (Unaudited)

The following unaudited pro forma summary presents consolidated information of the Company, including Sunosi, as if the business combination had occurred on January 1, 2022, the earliest period presented herein:

	Year ended December 31, 2022
Net revenues	$ 74,065
Net loss	(211,571)

Note 4. Accounts Receivable, net

Accounts receivable, net, consisted of the following:

	December 31, 2024	December 31, 2023
Trade receivables	$ 155,505	$ 107,320
Less: Reserves for variable consideration	(13,504)	(12,500)
Accounts receivable, net	$ 142,001	$ 94,820

Note 5. Inventory

Inventory consisted of the following:

	December 31, 2024	December 31, 2023
Raw materials	$ 9,541	$ 5,534
Work in process	7,723	10,287
Finished goods	8,986	9,643
Total	$ 26,250	$ 25,464

There were no material inventory reserves or write downs of any excess and obsolete inventory as of December 31, 2024. Non-current inventory, which consists of raw materials and work in progress inventory, is included in non-current inventory and other assets on the accompanying consolidated balance sheets. Non-current inventory is estimated to be consumed beyond the next 12 months.

The following table summarizes the balance sheet classification of the Company's inventory for each of the periods indicated:

	December 31, 2024	December 31, 2023
Balance sheet classification		
Inventories, net	$ 15,732	$ 15,135
Non-current inventory and other assets	10,518	10,329
Total	$ 26,250	$ 25,464

Note 6. Goodwill

The following table provides the Company's carrying amount of goodwill as of December 31, 2024.

	Goodwill
Balance at December 31, 2023	$ 12,042
Additions/adjustments	—
Balance at December 31, 2024	$ 12,042

Note 7. Intangible Asset

The following table provides the Company's carrying amount of the intangible asset for each of the periods indicated.

	Gross carrying amount	Accumulated amortization	Net carrying amount	Remaining weighted-average useful life
Balance at December 31, 2023				
Finite-lived intangible asset	$ 63,800	$ 10,514	$ 53,286	9-years
Balance at December 31, 2024				
Finite-lived intangible asset	$ 63,800	$ 16,906	$ 46,894	8-years

Based on the finite-lived intangible asset recorded as of December 31, 2024, and assuming the underlying asset will not be impaired and that the Company will not change the expected life of the asset, future amortization expense over the next five years and periods thereafter are estimated to be as follows:

	Estimated amortization expense
2025	$ 6,375
2026	6,375
2027	6,375
2028	6,392
2029	6,375
Thereafter	15,002
Total	$ 46,894

Note 8. Fair Value of Financial Instruments

In connection with the Acquisition, the Company pays royalty on U.S. net sales of Sunosi to Jazz. The discounted cash flow method used to value this contingent consideration includes inputs of not readily observable market data, which are Level 3 inputs. The fair value of the contingent consideration is reflected as current accrued contingent consideration of $8.3 million and non-current contingent consideration liability of $91.7 million in the consolidated balance sheet as of December 31, 2024.

The fair value of financial instruments measured on a recurring basis is as follows:

	December 31, 2024			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash and cash equivalents - money market funds	$ 244,097	$ —	$ —	$ 244,097
Liabilities:				
Contingent consideration	$ —	$ —	$ 99,965	$ 99,965

	December 31, 2023			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash and cash equivalents - money market funds	$ 251,768	$ —	$ —	$ 251,768
Liabilities:				
Contingent consideration	$ —	$ —	$ 79,707	$ 79,707

Contingent Consideration Liabilities

The fair value of the contingent consideration liabilities is marked-to-market each reporting period and was remeasured at December 31, 2024. Changes in fair value of the contingent consideration liabilities as of December 31, 2024 are as follows:

	Contingent consideration
Balance at December 31, 2023	$ 79,707
Adjustment to fair value	28,124
Payments	(7,866)
Balance at December 31, 2024 (Level 3)	$ 99,965

The recurring Level 3 fair value measurements of contingent consideration for which a liability is recorded include the following significant unobservable inputs:

			As of December 31, 2024	As of December 31, 2023
	Valuation methodology	Significant unobservable input	Weighted average (range, if applicable)	Weighted average (range, if applicable)
Contingent consideration	Probability weighted income approach	Discount rate	12.0%	13.2%
		Revenue discount rate	17.6% - 20.6%	16.4% - 19.4%

The Company's fair value measurement of contingent consideration liabilities has been classified as Level 3 as its valuation requires substantial judgment and estimation of factors which requires use of unobservable inputs. The fair value of contingent consideration liabilities are estimated by using the probability weighted income approach using significant assumptions including estimated future sales of Sunosi in current and future indications, timing of regulatory and commercial milestone achievements, probability of technical and regulatory success rates, and discount rates. If significant changes are made to one or more of these assumptions, the estimated fair value of contingent consideration liabilities may result in a significantly higher or lower fair value measurement.

Note 9. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31, 2024	December 31, 2023
Accrued research and development	$ 14,431	$ 6,503
Accrued compensation	28,225	20,457
Accrued selling, general, and administrative	17,498	9,242
Accrued sales discounts, rebates, and allowances	73,952	46,713
Accrued royalties	9,958	5,927
Accrued interest	1,542	1,659
Accrued taxes	960	—
Finance lease liability, current	1,421	—
Total	$ 147,987	$ 90,501

Note 10. Loan and Security Agreement

Hercules Capital, Inc.

For the purposes of this Note 10, capitalized terms used but not otherwise defined herein shall have the meanings assigned to them in the Loan Agreement (as defined below).

Fifth Amendment to the Loan Agreement

On September 30, 2024, the Company entered into a Fifth Amendment (the "Fifth Amendment") to its Loan and Security Agreement, dated as of September 25, 2020 (as amended by that certain First Amendment to Loan and Security Agreement, dated as of October 14, 2021, as further amended by the Second Amendment to Loan and Security Agreement, dated as of March 27, 2022, as further amended by the Third Amendment to Loan and Security Agreement, dated as of January 9, 2023, and as further amended by the Waiver and Fourth Amendment to Loan and Security Agreement, dated as of May 8, 2023) (the "Loan Agreement") with Hercules Capital, Inc., a Maryland corporation ("Hercules"), in its capacity as administrative agent and collateral agent, and the other financial institutions or entities party thereto as lenders (collectively, the "Lenders"), with respect to the term loan thereunder (the "2020 Term Loan").

The Fifth Amendment amended the terms of the Loan Agreement to, among other things: (i) increase the Tranche 3 Commitment from $75.0 to $80.0 million; (ii) extend the availability periods of Tranche 1D to June 15, 2025 and that of Tranche 1E to December 15, 2025, as set forth in greater detail in the Fifth Amendment; (iii) alter the terms of Performance Covenant A, Performance Covenant B, and Performance Covenant C and also add a Performance Covenant D, as set forth in greater detail in the Fifth Amendment; (iv) conditionally waive the requirement that the Company maintain Qualified Cash in an amount greater than or equal to the sum of $30.0 million plus the Qualified Cash A/P Amount at all times during such periods of time that the Company's Market Capitalization exceeds $1.5 billion; and (v) permit Axsome Malta Ltd. ("Axsome Malta") to request an Advance from the Lenders up to a certain amount to the extent that the Company may request an Advance in such amount and to increase the amount of Cash that Axsome Malta may hold outside of the United States, as set forth in greater detail in the Fifth Amendment.

The Waiver and Fourth Amendment (the "Fourth Amendment") to the Loan Agreement with Hercules and the Third Amendment (the "Third Amendment") to the Loan Agreement with Hercules incorporate the following amendments:

- The increase of cash held by Axsome Malta outside of the United States from $3.0 million to $15.0 million for a 45-day period after the closing of the Fourth Amendment and to $10.0 million thereafter;
- The waiver of any purported default with respect to the amount of cash held by Axsome Malta prior to the date of the Fourth Amendment;
- In August 2023, Hercules granted the Company a waiver to the Fourth Amendment, permitting Axsome Malta to hold up to $12.5 million in Cash outside of the United States until December 31, 2023;
- Extend the maturity date to January 1, 2028, unless the Company meets certain revenue targets as described in the Loan Agreement, in which case the Company can extend the maturity date to January 1, 2029;
- Increase the aggregate principal amount under the Loan Agreement from $300.0 million to $350.0 million;
- Subject to the terms and conditions in the Loan Agreement, change the term loan advance amounts and availability dates under the Tranche 1 Advance through Tranche 5 Advance, including increasing the Tranche 1 Advance from one tranche of $95.0 million to five sub-tranches of $95.0 million, $55.0 million, $30.0 million, $35.0 million, and $35.0 million, respectively, changing the Tranche 2 Advance from three sub-tranches of $35.0 million, $35.0 million, and $30.0 million, respectively, to one tranche of $25.0 million, changing the Tranche 3 Advance from two sub-tranches of $15.0 million and $5.0 million, respectively, to one tranche of $75.0 million, and removing the Tranche 4 Advance and Tranche 5 Advance entirely;
- Revise the interest rate applicable to extensions of credit under the Loan Agreement to equal (a) if the prime rate is greater than or equal to 7.00%, the greater of either (i) the prime rate plus 2.20%, and (ii) 9.95%, but in no event greater than 10.70%, and (b) if the prime rate is less than 7.00%, 9.70%;
- Increase the minimum cash requirement of the Company to the sum of $30.0 million plus the Qualified Cash A/P Amount; and
- Require the Company to pay a facility fee equal to 0.75% of the amount of principal actually funded pursuant to the Tranche 1B Advance, Tranche 1C Advance, Tranche 1D Advance, Tranche 1E Advance, Tranche 2 Advance, and Tranche 3 Advance.

As of December 31, 2024, the Company had allowed Tranche 2, which totaled $25.0 million, to expire undrawn.

On October 14, 2021, the Company entered into a First Amendment to the Loan and Security Agreement with Hercules. On March 27, 2022, in connection with the Acquisition (as described above), the Company entered into a Second Amendment to the Loan and Security Agreement (the "Second Amendment") with Hercules. The Second Amendment closed on May 9, 2022, concurrently with the closing of the Acquisition.

As collateral for the obligations, the Company has granted to Hercules a senior security interest in all of the Company's right, title, and interest in, to and under all of the Company's property, inclusive of intellectual property, which includes one of the Company's existing license agreements (the "License Agreement") with Antecip, an entity owned by Axsome's Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., subject to limited exceptions. Antecip consented to the collateral assignment of the License Agreement, among other things, under a direct agreement (the "Direct Agreement") with the Company, Antecip and Hercules.

The Loan Agreement contains customary representations, warranties and covenants, including covenants by the Company limiting additional indebtedness, liens (including a negative pledge on intellectual property and other assets), guaranties, mergers and consolidations, substantial asset sales, investments and loans, certain corporate changes, transactions with affiliates and fundamental changes. At the initial closing, there were no applicable financial covenants contained in the Loan Agreement. Effective upon closing of the Fifth Amendment in September 2024, the following limited financial covenants apply:

- The Company at all times must maintain Qualified Cash in an aggregate amount greater than or equal to $30.0 million plus the Qualified Cash A/P Amount; provided that compliance with such covenant shall be conditionally waived during such periods of time that the Company's Market Capitalization exceeds $1.5 billion.
- The Company must meet, beginning June 30, 2023, any of the following conditions: (A) ensure that at all times its market capitalization exceeds $1.0 billion and that it maintains Qualified Cash in an amount not less than 30% of the sum of the outstanding principal amount of the Term Loan Advances plus the Qualified Cash A/P Amount, (B) ensure that at all times that it maintains Qualified Cash in an amount not less than 50% of the sum of the outstanding principal amount of the Term Loan Advances plus the Qualified Cash A/P Amount, or (C) ensure that at all times its market capitalization exceeds $1.5 billion. Alternatively, the Company must, beginning with fiscal quarter ending September 30, 2024, and for each quarter thereafter, achieve T6M Net Product Revenue in an amount equal to at least the amount set forth on Schedule 7.20(b) of the Loan Agreement opposite the last day of each fiscal quarter identified in the table therein, tested on a quarterly basis.
- Axsome Malta, a company organized under the laws of the Republic of Malta, may request an Advance from the Lenders up to a certain amount to the extent that the Company may request an Advance in such amount, and Axsome Malta may not hold Cash outside of the United States in excess of the sum of $10.0 million and the aggregate outstanding principal amount of Advances drawn by Axsome Malta.
- Restrictions on the Company's ability to incur additional indebtedness, pay dividends, encumber its intellectual property, or engage in certain fundamental business transactions, such as mergers or acquisitions of other businesses, with certain exceptions.

The Company's obligations under the Loan Agreement are subject to acceleration upon the occurrence of specified events of default, including payment default, insolvency and a material adverse change in the Borrower's business, operations or financial or other condition.

In addition, the Company is required to pay certain end of term charges, including (A) an initial end of term charge of $4.45 million and (B) a subsequent end of term charge of (i) 1.10% of the aggregate amount of all Tranche 1A Advances plus (ii) 4.95% of the aggregate amount of all term loan advances (other than Tranche 1A Advances) funded minus (iii) any charges paid by the Borrower to the Lenders related to partial prepayments of the outstanding Secured Obligations. The end of term charges are being accreted into interest expense using the effective interest rate method over the term of the loan.

If certain maturity extension conditions are satisfied, the Company must pay an extension end of term charge equal to 1.00% of the aggregate amount of all Term Loan Advances outstanding as of the date on which the maturity extension conditions are satisfied, in addition to the end of term charges described above.

The Company may, at its option prepay the term loans in full or in part, subject to a prepayment penalty equal to (i) 2.0% of the Advance amount prepaid if the prepayment occurs prior to February 1, 2024, (ii) 1.5% of the Advance amount prepaid if the prepayment occurs on or after February 1, 2024 but prior to February 1, 2025, and (iii) 1.0% of the Advance amount prepaid if the prepayment occurs on or after February 1, 2025 but prior to February 1, 2026.

The Company evaluated whether the Third Amendment entered into in January 2023 represented a debt modification or extinguishment in accordance with ASC 470-50, *Debt – Modifications and Extinguishments*. As the present value of the cash flows under the terms of the Third Amendment is less than 10% different from the remaining cash flows under the terms of the Second Amendment, the Third Amendment was accounted for as a debt modification. The unamortized balance of debt discount costs incurred in connection with those loans and additional debt discount costs incurred in connection with entry into the Third Amendment are being amortized through maturity in January 2028 utilizing the effective interest rate method.

The Company also evaluated whether the Fifth Amendment entered into September 2024 represented a debt modification or extinguishment in accordance with ASC 470. As the terms of the Fifth Amendment are not substantially different as compared to that of the Fourth Amendment, the Company treated the amendment as a debt modification.

Loan Interest Expense and Amortization

Long-term debt and unamortized debt discount balances are as follows:

	December 31, 2024	December 31, 2023
Total outstanding debt	$ 180,000	$ 180,000
Add: accreted final payment fee	4,085	2,610
Less: unamortized debt discount, long-term	(3,375)	(4,540)
Less: current portion of long-term debt	—	—
Loan payable, long-term	$ 180,710	$ 178,070

The book value of debt approximates its fair value given its variable interest rate.

Interest expense, amortization of the final payment fee, amortization of the debt discount related to the issuance costs and warrants for the Company's debt are as follows:

	Year ended December 31,		
	2024	2023	2022
Interest expense	$ 19,254	$ 17,514	$ 8,176
Amortization of final payment fee	1,475	1,197	668
Amortization of debt discount related issuance costs and warrants	1,165	1,324	815

Scheduled principal payments on outstanding debt, as of December 31, 2024, are as follows:

2025	$ —
2026	—
2027	—
2028	180,000
2029	—
Thereafter	—
Total principal payments outstanding	$ 180,000

Note 11. Commitments and Contingencies

Leases

Leases are accounted for under ASC Topic 842. The Company made an accounting policy election not to apply the recognition requirements to short-term leases. The Company recognizes the lease payments for short-term leases in the consolidated statements of operations on a straight-line basis over the lease term, and variable lease payments in the period in which the obligation for those payments is incurred. Therefore, the Company is not recognizing a lease liability or right-of-use asset for any lease that, at the commencement date, has a lease term of 12 months or less and does not include an option to extend the term or purchase the underlying asset that the Company is reasonably certain to exercise. The Company's lease terms may include options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. The Company has entered into a lease agreement for the Company's principal executive offices located in New York, NY. The lease does not include any restrictions or covenants that had to be accounted for under the lease guidance.

In February 2023, the Company entered into a ten-year agreement to sublease office space at One World Trade Center, which began in April 2023. Based on the Company's past experience and current expectation for administrative office needs, the Company determined the lease term to be five years. As of December 31, 2024, the remaining lease term for the Company's operating lease was 3.3 years with the discount rate of 12.0%. The interest rate implicit in lease contracts is typically not readily determinable and as such, the Company uses its incremental borrowing rate based on the information available at the lease commencement date, which represents an internally developed rate that would be incurred to borrow, on a collateralized basis, over a similar term, an amount equal to the lease payments in a similar economic environment.

The Company entered into a fleet lease program beginning the first quarter of 2024. The lease agreement includes an initial 12-month noncancelable period with monthly renewal options thereafter. Lease terms range from approximately 40 to 50 months and are classified as finance leases. During the year ended December 31, 2024, the Company recognized a right-of-use asset and lease liability, both, of $5.4 million in connection to this lease. As of December 31, 2024, right-of-use asset and lease liability related to the finance lease were $4.3 million and $4.4 million, respectively, and the weighted average remaining lease term was 3.1 years, with a weighted average discount rate of 9.0%.

Lease expenses recognized were as follows:

	Year ended December 31,		
	2024	2023	2022
Operating lease expense	$ 2,331	$ 2,173	$ 1,208
Finance lease expense:			
Amortization of right-of-use assets	1,034	—	—
Interest on lease liabilities	320	—	—

Future minimum lease payments of the Company's leases as of December 31, 2024, were as follows:

	Operating lease	Finance lease
2025	$ 1,789	$ 1,741
2026	2,521	1,638
2027	2,521	1,167
2028	3,204	403
2029	—	1
Thereafter	—	—
Total lease payments	10,035	4,950
Less imputed interest	(2,154)	(585)
Present value of lease liabilities	$ 7,881	$ 4,365

Note 12. Stockholders' Equity

Public Offerings

At-the-Market Offerings

In December 2019, the Company entered into a sales agreement (the "December 2019 Sales Agreement") with SVB Securities LLC (now known as Leerink Partners LLC) ("Leerink"), pursuant to which the Company may sell up to $80 million in shares of the Company's common stock from time to time through Leerink, acting as the Company's sales agent, in one or more at-the-market offerings utilizing an automatic shelf registration statement (the "2019 Shelf Registration Statement") the Company filed with the U.S. Securities and Exchange Commission (the "SEC") on December 5, 2019 for the issuance of common stock, preferred stock, warrants, rights, debt securities and units. Leerink is entitled to receive a commission of 3.0% of the gross proceeds for any shares sold under the December 2019 Sales Agreement. The December 2019 Sales Agreement was replaced by the March 2022 Sales Agreement (as defined below).

In March 2022, the Company entered into a sales agreement (the "March 2022 Sales Agreement") with Leerink and filed a prospectus supplement, pursuant to which the Company could sell up to $200 million in shares of the Company's common stock from time to time through Leerink, acting as the Company's sales agent, in one or more at-the-market offerings utilizing the 2019 Shelf Registration Statement. Leerink is entitled to receive a commission of up to 3.0% of the gross proceeds for any shares sold under the March 2022 Sales Agreement. The March 2022 Sales Agreement supersedes the December 2019 Sales Agreement, dated December 5, 2019, by and between the Company and Leerink. The Company exhausted sales of shares of the Company's common stock under its prior at-the-market offering program.

In August 2022, the Company filed a prospectus supplement to the 2019 Shelf Registration Statement for the issuance and sale, if any, of up to an additional $250 million in shares of the Company's common stock. The Company will pay Leerink a commission of up to 3.0% of the gross sales proceeds of any shares sold through Leerink, acting as sales agent, under the March 2022 Sales Agreement.

In December 2022, in connection with the 2022 Shelf Registration Statement (as defined below), the Company filed a new sales agreement prospectus to replace the prior prospectus supplement filed in August 2022 associated with the expired 2019 Shelf Registration Statement. The new sales agreement prospectus covered the issuance and sale by the Company of up to the same $250 million of the Company's common stock that may be issued and sold from time to time through Leerink, as the Company's sales agent, under the March 2022 Sales Agreement.

Under the March 2022 Sales Agreement, for the three months ended December 31, 2024, the Company received approximately $16.4 million in gross proceeds through the sale of 168,973 shares, of which net proceeds were approximately $16.1 million. For the year ended December 31, 2024, the Company received approximately $40.8 million in gross proceeds through the sale of 466,108 shares, of which net proceeds were approximately $40.0 million, under the March 2022 Sales Agreement. The Company did not utilize the March 2022 Sales Agreement with Leerink during the year ended December 31, 2023.

Under the December 2019 Sales Agreement and March 2022 Sales Agreement, the Company received approximately $238.8 million in gross proceeds through the sale of 5,167,973 shares, of which net proceeds were approximately $231.8 million for the year ended December 31, 2022.

Upon the closing of the Second Amendment, which occurred in March 2022, Hercules also purchased 152,487 of the Company's unregistered common stock for a total consideration of $5.0 million at a share price equal to $32.79 per share, pursuant to a share transfer agreement.

The holders of shares of common stock are entitled to one vote for each share of common stock held at all meetings of stockholders and written actions in lieu of meetings. The holders of shares of common stock are entitled to receive dividends, if and when declared by the Board.

June 2023 Public Offering

In June 2023, the Company completed an underwritten public offering of its common stock (the "June 2023 Public Offering"). The Company sold 3.0 million shares of its common stock at a public offering price of $75.00 per share. The net proceeds were $211.3 million, net of underwriting discounts and commissions of $13.5 million and other offering costs of $0.2 million. Additionally, in connection with this public offering, in July 2023, the underwriters fully exercised their option to purchase 450,000 additional shares of the Company's common stock at a public offering price of $75.00 per share. The net proceeds from the exercise of the option were $31.7 million, net of underwriting discounts and commissions of $2.0 million and other minimal offering costs.

Shelf Registration Statement

On December 2, 2022, the Company filed an automatic shelf registration statement (the "2022 Shelf Registration Statement") with the SEC for the issuance of common stock, preferred stock, warrants, rights, debt securities and units. It became effective upon filing with the SEC and is currently the Company's only active shelf registration.

Under SEC rules, the 2022 Shelf Registration Statement allows for the potential future offer and sale by the Company, from time to time, in one or more public offerings of an indeterminate amount of the Company's common stock, preferred stock, debt securities, and units at indeterminate prices. At the time any of the securities covered by the 2022 Shelf Registration Statement are offered for sale, a prospectus supplement will be prepared and filed with the SEC containing specific information about the terms of any such offering.

Equity Incentive Plan

In November 2015, the 2015 Omnibus Incentive Compensation Plan (the "2015 Plan") was adopted by the Company's stockholders. As of December 31, 2024, there were 2,997,349 shares available for future grant under the 2015 Plan.

Stock Options

The following table sets forth stock option activity as of December 31, 2024:

	Number of shares	Weighted average exercise price	Weighted average contractual term (years)	Aggregate intrinsic value
Outstanding at December 31, 2023	8,462,294	$ 41.48		
Granted	1,220,294	84.13		
Exercised	(718,163)	38.21		
Forfeited/Canceled	(525,304)	60.83		
Outstanding at December 31, 2024	8,439,121	$ 46.72	6.5	$ 321,478
Vested and expected to vest at December 31, 2024	8,439,121	$ 46.72	6.5	$ 321,478
Exercisable at December 31, 2024	5,368,481	$ 35.52	5.4	$ 263,725

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option pricing model. The expected term of the Company's stock options has been determined utilizing the "simplified" method as described in the SEC's Staff Accounting Bulletin No. 107 relating to stock-based compensation. The simplified method was chosen because the Company has limited historical option exercise experience due to its short operating history. The risk-free interest rate is based on the U.S. Treasury yield in effect at the time of grant for a period approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future. In prior years, expected volatility was based on historical volatilities of similar entities within the Company's industry which were commensurate with the Company's expected term assumption. Currently, expected volatility is based on historical volatility information of the Company's common stock since the Company's initial public offering in 2015.

The relevant data used to determine the value of the stock option grants is as follows:

Black-Scholes option valuation assumptions	2024	2023	2022
Risk-free interest rates	3.51 - 4.62%	3.34 - 4.88%	1.46 - 4.31%
Dividend yield	—	—	—
Volatility	81 - 93%	93 - 99%	90 - 95%
Weighted average expected term	5.0 - 6.11 years	5.0 - 6.11 years	5.0 - 6.11 years

The weighted average grant date fair value of options granted was $64.88, $53.07 and $28.18 per option for the years ended December 31, 2024, 2023 and 2022, respectively. As of December 31, 2024, there was $146.6 million of total unrecognized compensation cost related to non-vested stock options which is expected to be recognized over a weighted average period of 2.3 years.

Restricted Stock Units

The fair value of RSUs is determined on the date of the grant based on the market price of its shares of common stock as of that date. The fair value of the RSUs is recognized as an expense ratably over the vesting period of four years. As of December 31, 2024, total compensation cost not yet recognized related to unvested RSUs was $42.0 million, which is expected to be recognized over a weighted-average period of 2.4 years. The intrinsic value of RSUs lapsed during the years ended December 31, 2024, 2023 and 2022 was $10.3 million, $4.9 million and $1.5 million, respectively.

The following table sets forth the RSU activity for the year ended December 31, 2024:

	Number of shares	Weighted average grant date fair value
Outstanding at December 31, 2023	804,150	$ 41.36
Granted	471,778	77.50
Vested	(267,779)	39.41
Forfeited	(101,205)	52.76
Outstanding at December 31, 2024	906,944	$ 59.48

Employee Stock Purchase Plan

The ESPP allows eligible employees to purchase shares of the Company's common stock. The purchase price is equal to 85% of the lower of the closing price of the Company's common stock on (1) the first day of the offering period or (2) the last day of the offering period. The ESPP has consecutive offering periods that begin on or about June 1st of each year with a duration of 12 months. The Company commenced the first offering period pursuant to the ESPP on June 1, 2023, and such offering ended on May 31, 2024.

As of December 31, 2024, 52,368 common shares have been purchased and issued pursuant to the ESPP, and $1.6 million of expense was recorded for the year ended December 31, 2024. During the year ended December 31, 2023, no shares of common stock were purchased pursuant to the ESPP, and $1.1 million of expense was recorded.

Stock-based Compensation Expense

Stock-based compensation expense recognized was as follows:

	Year ended December 31,		
	2024	2023	2022
Research and development	$ 21,417	$ 14,080	$ 8,604
Selling, general and administrative	63,801	48,540	29,122
Total	$ 85,218	$ 62,620	$ 37,726

Stock-based compensation expense capitalized into inventory totaled $1.3 million, $2.7 million, and $1.3 million for the years ended December 31, 2024, 2023, and 2022, respectively. The Company started capitalizing stock-based compensation to inventory in the third quarter of 2022. Capitalized stock-based compensation is recognized as an expense in cost of product sales when the related product is sold or in selling, general and administrative expense when the related product is dispensed as a physician sample.

Note 13. Warrants

The following table summarizes warrant activity for the years ended December 31, 2024, 2023, and 2022:

	Warrants	Weighted average exercise price
Outstanding at December 31, 2021	15,541	$ 80.43
Issued	35,255	31.91
Exercised	—	—
Outstanding at December 31, 2022	50,796	$ 46.75
Issued	28,424	74.75
Exercised	—	—
Outstanding at December 31, 2023	79,220	$ 56.80
Issued	—	—
Exercised	—	—
Outstanding at December 31, 2024	79,220	$ 56.80

Outstanding Warrants

In connection with the entry into the Third Amendment, Hercules received warrants to purchase an aggregate of 18,724 shares of the Company's common stock at an exercise price of $55.01 per share, and in connection with the draw down of the Tranche 1C Advance, Hercules received warrants to purchase 9,700 shares of the Company's common stock at an exercise price of $77.31 per share (collectively, the "2023 warrants"). In connection with the entry into the Second Amendment, Hercules received warrants to purchase an aggregate of 35,255 shares of the Company's common stock at an exercise price of $31.91 per share (the "2022 warrants"), and in connection with the first advance of the 2020 Term Loan, Hercules received warrants to purchase an aggregate of 15,541 shares of the Company's common stock at an exercise price of $80.43 per share (the "2020 warrants").

The 2023 warrants, 2022 warrants and 2020 warrants were priced using the volume weighted average price of the Company's common stock over the ten-day trading period immediately preceding the initial closing, subject to certain limited adjustments as specified in the warrant. The warrants are exercisable for seven years from the date of issuance. The warrants were classified as a component of stockholders' equity. The relative fair value of the warrants of approximately $1.6 million for the 2023 warrants, $0.8 million for the 2022 warrants and $0.9 million for the 2020 warrants at the time of issuance, which was determined using the Black-Scholes option-pricing model, was recorded as additional paid-in capital and reduced the carrying value of the debt. The discount on the debt is being amortized to interest expense over the term of the debt utilizing the effective interest rate method.

The initial fair value of warrants outstanding was estimated using the Black-Scholes option pricing model with the following assumptions:

Black-Scholes option valuation assumptions	2023 warrants	2022 warrants	2020 warrants
Risk-free interest rate	3.6 - 3.9%	3.1%	0.5%
Dividend yield	—	—	—
Volatility	92 - 95%	94%	88%
Weighted average contractual term	7 years	7 years	7 years

Note 14. Net Loss per Common Share

The following table sets forth the computation of basic and diluted net loss per common share:

	Year ended December 31,		
	2024	2023	2022
Basic and diluted net loss per common share:			
Net loss	$ (287,216)	$ (239,238)	$ (187,134)
Weighted average common shares outstanding—basic and diluted	47,914,253	45,425,212	40,655,941
Net loss per common share—basic and diluted	$ (5.99)	$ (5.27)	$ (4.60)

The following potentially dilutive securities have been excluded from the computation of diluted weighted average shares outstanding, as they would be anti-dilutive:

	December 31,		
	2024	2023	2022
Stock options	8,439,121	8,462,294	6,617,728
Restricted stock units	906,944	804,150	686,375
Warrants	79,220	79,220	50,796
ESPP	64,886	56,760	—
Total	9,490,171	9,402,424	7,354,899

Note 15. Revenues

The Company sells Auvelity and Sunosi in the United States through the Distributors. The Company also sells Sunosi to Distributors in Canada and on a product supply basis to Pharmanovia. Sunosi is subsequently sold by Pharmanovia in certain ex-U.S. markets. For the year ended December 31, 2024, the Company's three largest customers represented approximately 35%, 29%, and 28% of the Company's gross product sales.

License revenue consists of the recognition of the upfront payment the Company received from Pharmanovia in February 2023, royalty revenue related to the sales of Sunosi by Pharmanovia in certain ex-U.S. markets, and a milestone revenue of $0.5 million related to an achievement of a regulatory milestone in China for Sunosi from SK recorded in the fourth quarter of 2024.

The following table presents a summary of total revenues by product:

	Year ended December 31,		
	2024	2023	2022
Product sales, net			
Auvelity	$ 291,378	$ 130,072	$ 5,168
Sunosi	90,299	72,388	44,869
Total product sales, net	381,677	202,460	50,037
Sunosi license revenue	—	65,735	—
Sunosi royalty and milestone revenue	4,016	2,405	—
Total revenues	$ 385,693	$ 270,600	$ 50,037

The following table presents a summary of total revenues by geographic location:

	Year ended December 31,		
	2024	2023	2022
Product sales, net			
United States	$ 378,159	$ 197,224	$ 49,132
Outside of the United States	3,518	5,236	905
Total product sales, net	381,677	202,460	50,037
License revenue			
Outside of the United States	—	65,735	—
Royalty and milestone revenue			
Outside of the United States	4,016	2,405	—
Total revenues	$ 385,693	$ 270,600	$ 50,037

For the year ended December 31, 2024, product sales, net, includes adjustments for provisions for product sales made in 2023 resulting from changes in estimates of $0.8 million for Auvelity and $0.6 million for Sunosi. For the year ended December 31, 2023, product sales, net, includes adjustments for provisions for product sales made in 2022 resulting from changes in estimates of $0.8 million for Auvelity and $0.1 million for Sunosi.

Note 16. License Agreements

License Agreement with Pharmanovia

In February 2023, Axsome Malta, a Malta limited company and a wholly-owned subsidiary of the Company, entered into an exclusive license agreement with Pharmanovia (the "Pharmanovia License Agreement") to commercialize and further develop Sunosi in Europe and certain countries in the Middle East and North Africa (the "Territory"). Under the terms of the Pharmanovia License Agreement, the Company retains its existing interest in Sunosi intellectual property and licenses those rights in the Territory to Pharmanovia. Pharmanovia is solely responsible for the clinical development and commercialization of Sunosi in the Territory. The Company will continue to manufacture Sunosi and provide product supply to Pharmanovia for an indefinite period of time, and the Company will recognize revenue as a component of product sales, net, when product is supplied to Pharmanovia.

In consideration for entering the Pharmanovia License Agreement, the Company received a non-refundable upfront payment of €62.0 million ($65.7 million). The Company also will receive a royalty percentage in the mid-twenties on Sunosi net sales in the Territory and is eligible to receive sales-based milestone payments totaling up to €94.5 million.

The Company evaluated the Pharmanovia License Agreement under ASC 606 and concluded that Pharmanovia represents a customer in the transaction. The initial transaction price consisted of the non-refundable upfront payment, which was recognized as License Revenue in the first quarter of 2023 upon transfer of the license to Pharmanovia, as the requirement for revenue recognition under ASC 606 were met. The remaining forms of consideration are variable because they are dependent on the achievement of sales-based or other milestones. The Company evaluated the constraint on variable consideration and concluded that the milestone payments are dependent on regulatory approvals and actions of third parties, and thus are highly susceptible to factors outside the Company's influence. Therefore, at contract inception, the milestones are not included in the transaction price as it is not probable that a significant reversal of revenue would not occur. Sales-based milestones will be recognized as revenue in the period when the related sales threshold is met. All other development or regulatory milestones will be recognized as revenue immediately in the period the underlying milestone is achieved. Any consideration related to sales-based royalties will be recognized when the related sales occur. For the year ended December 31, 2024, the Company recognized royalty revenue of $3.5 million related to Pharmanovia's sales of Sunosi, and $0.5 million related to an achievement of a regulatory milestone in China for Sunosi from SK in the fourth quarter of 2024. No other development or sales-based milestones were recognized during the year ended December 31, 2024.

Exclusive License Agreement with Pfizer

In January 2020, the Company entered into an exclusive license agreement with Pfizer Inc. ("Pfizer") for Pfizer's clinical and nonclinical data, and intellectual property for reboxetine, the active pharmaceutical ingredient in AXS-12 which the Company is developing for the treatment of narcolepsy. The agreement also provides the Company exclusive rights to develop and commercialize esreboxetine, a new late-stage product candidate referred to as AXS-14, in the U.S. for the treatment of fibromyalgia.

Under the terms of the agreement, Pfizer received 82,019 shares of the Company's common stock having a stated value of $8.0 million, based on the average closing price of the Company's common stock for the ten prior trading days of $97.54, in consideration for the license and rights and also received an upfront cash payment of $3.0 million. The Company determined that the fair value of each share of common stock granted to Pfizer on the closing date of January 9, 2020 was $87.24, based on the closing price of the Company's stock on that date. As a result, the fair value of the stock issued was $7.2 million and, therefore, the total research and development expense recognized was $10.2 million related to the Pfizer license agreement during the year ended December 31, 2020.

Pfizer can also receive up to $323 million in regulatory and sales milestones, and tiered mid-single to low double-digit royalties on future sales related to the licensed products. Pfizer will also have a right of first negotiation on any potential future strategic transactions involving AXS-12 and AXS-14. During the years ended December 31, 2024 and 2023, no milestone payments or royalties were paid to Pfizer by the Company.

Exclusive License Agreements with Antecip

In 2012, the Company entered into three exclusive license agreements with Antecip, an entity owned by the Company's Chief Executive Officer and Chairman of the Board, Herriot Tabuteau, M.D., in which the Company was granted exclusive licenses to develop, manufacture and commercialize Antecip's patents and applications related to the development of AXS-05 (now marketed as Auvelity) and two product candidates no longer under active development, anywhere in the world for human therapeutic, veterinary, and diagnostic use. Pursuant to the agreements, the Company is required to use commercially reasonable efforts to develop, obtain regulatory approval for and commercialize these product candidates. Under the terms of the agreements, the Company is required to pay to Antecip a royalty equal to 3.0% for AXS-05 (and 1.5% or 4.5% for the other two product candidates no longer under active development), of net sales of products containing the licensed technology by the Company, its affiliates, or permitted sublicensees. These royalty payments are subject to reduction by an amount up to 50.0% of any required payments to third parties. Unless earlier terminated by a party for cause or by the Company for convenience, the agreements shall remain in effect on a product-by-product and country-by-country basis until the later to occur of (i) the applicable product is no longer covered by a valid claim in that country or (ii) 10 years from the first commercial sale of the applicable product in that country. Upon expiration of the agreements with respect to a product in a country, the Company's license grant for that product in that country will become a fully paid-up, royalty-free, perpetual non-exclusive license. If Antecip terminates any of the agreements for cause, or if the Company exercises its right to terminate any of the agreements for convenience, the rights granted to the Company under such terminated agreement will revert to Antecip. The Company began recording royalty payments to Antecip along with the initiation of sales of Auvelity (the components of which are referred to as "AXS-05") in the fourth quarter of 2022. For the year ended December 31, 2024, the Company recorded royalty expense of $8.7 million for royalty due to Antecip, which is equal to 3.0% of net sales of Auvelity. This is considered to be a related party transaction.

In connection with the Loan Agreement, the Company entered into the Direct Agreement with Antecip and Hercules, pursuant to which Antecip consented to the collateral assignment of the License Agreement under the Loan Agreement, among other things.

Note 17. Royalty Agreements

Pursuant to the Purchase Agreement, the Company agreed to make non-refundable, non-creditable royalty payments to Jazz equal to a (A) high single-digit royalty for any current indication, or (B) mid single-digit royalty for any future indication of net sales in the U.S. Territory made during the applicable royalty term. There are no royalty payments due to Jazz for Net Sales outside of the U.S. Territory.

At the Initial Closing, the Company assumed all of the commitments of Jazz to SK and Aerial. SK is the originator of Sunosi and retains rights in 12 Asian markets, including China, Korea and Japan. In 2014, Jazz acquired from Aerial worldwide rights to Sunosi excluding those Asian markets stated previously. The assumed commitments to SK and Aerial include single-digit tiered royalties based on the Company's sales of Sunosi, and additionally, the Company is committed to pay up to $165 million based on revenue milestones and $1 million based on development milestones. In the fourth quarter of 2024, the Company recorded a $2.5 million expense for the achievement of a sales-based milestone related to world-wide Sunosi sales.

Note 18. Income Taxes

As of December 31, 2024, the Company has U.S. federal net operating loss ("NOL") carryforwards of approximately $572.1 million and foreign NOL carryforwards of $4.8 million. U.S. federal NOLs amounting to $59.8 million generated before the 2018 tax year will start expiring beginning 2032, and the NOLs of approximately $512.3 million generated in 2018 and later have an indefinite carryforward period. The NOL carryforwards are subject to review and possible adjustment by the Internal Revenue Service ("IRS") and state tax authorities. NOL carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant stockholders, as defined under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, as well as similar state tax provisions. This could limit the amount of NOLs that the Company can utilize annually to offset future taxable income or tax liabilities.

The components of the Company's deferred tax assets and deferred tax liabilities are as follows:

	December 31, 2024	December 31, 2023
Deferred tax assets:		
Net federal operating loss carryforward	$ 120,149	$ 114,889
Net foreign operating loss carryforward	4,830	697
Net state operating loss carryforward	37,828	34,365
Non-cash compensation	30,734	20,007
Research and development credits	27,409	21,034
Interest expense	3,458	1,327
Intangible asset	5,547	4,242
Accrued expenses	9,180	6,058
Section 174 capitalization	42,343	22,248
Fixed assets	43	—
Lease liability	3,045	—
Other	4	315
Deferred tax asset, excluding valuation allowance	284,570	225,182
Deferred tax liabilities:		
Fixed assets	—	(78)
Lease asset	(2,413)	(1,661)
Deferred tax liability, excluding valuation allowance	(2,413)	(1,739)
Less valuation allowance	(282,157)	(223,443)
Net deferred tax assets	$ —	$ —

A valuation allowance is provided for deferred tax assets where the recoverability of the assets is uncertain. The determination to provide a valuation allowance is dependent upon the assessment of whether it is more likely than not that sufficient future taxable income will be generated to utilize the deferred tax assets. Based on the weight of the available evidence, which includes the Company's historical operating losses and forecast of future losses, the Company provided a full valuation allowance against the deferred tax assets resulting from the tax loss and credits carried forward. The valuation allowance increased by $58.7 million, $39.0 million and $26.9 million, in 2024, 2023 and 2022, respectively, as a result of the increase of the deferred tax assets.

For the year ended December 31, 2024, the Company recorded $0.1 million of income tax expense due to state taxes that the Company expects to pay based on minimum tax requirements in various states. For the year ended December 31, 2023, the Company recorded $1.0 million of income tax expense related to its foreign operations in Malta primarily due to a one-time payment received in connection with the Pharmanovia License Agreement. There was no income tax expense or benefit recorded by the Company in any other jurisdiction due to its net loss tax position and full valuation allowance during the year ended December 31, 2024, 2023, and 2022. As of December 31, 2024, the Company does not believe any material uncertain tax positions are present. A reconciliation of the statutory federal income tax rate to the Company's annual effective tax rate as reflected in the consolidated financial statements is as follows:

	December 31, 2024	December 31, 2023	December 31, 2022
U.S. federal statutory income tax rate	21.0%	21.0%	21.0%
State taxes, net of federal benefit	2.2	2.6	4.5
Foreign Rate Differential	(6.3)	(1.8)	1.2
Stock based compensation - Excess tax benefit	1.3	0.7	1.0
162(m) Limitation	(1.1)	(1.4)	—
Other permanent differences	(0.6)	(0.4)	(0.3)
Tax credit	2.8	1.9	(0.6)
Deferred tax adjustment	0.5	—	(2.9)
GILTI	—	(2.0)	—
Change in valuation allowance	(19.8)	(21.0)	(23.9)
Effective tax rate	—%	(0.4)%	—%

The Company is currently under examination by the IRS for the Company's 2021 U.S. income tax return. The Company is not currently under examination at the state level. The Company's U.S. federal and state net operating losses have occurred since its inception in 2012 and as such, tax years subject to potential tax examination could apply from that date because the utilization of net operating losses from prior years opens the relevant year to audit by the IRS and/or state taxing authorities.

The Company has elected to account for Global Intangible Low-Taxed Income (GILTI) in the period in which it is incurred, and therefore has not provided deferred tax impacts of GILTI in its consolidated financial statements.

Note 19. Related Party Transactions

From the Company's inception, Herriot Tabuteau, M.D. has been the Company's founder, Chief Executive Officer, Chairman of the Company's Board, and the beneficial owner of more than 5% of the outstanding shares of the Company's common stock. In connection with the formation of the Company, in January 2012, the Company issued to Antecip Bioventures II LLC, an entity controlled by Dr. Tabuteau, an aggregate of 7,344,500 shares of the Company's common stock for nominal consideration. Additionally, since the launch of Auvelity in the fourth quarter of 2022, the Company recorded royalty expense of $8.7 million and $3.9 million for the years ended December 31, 2024 and 2023, respectively, which equal 3.0% of net sales for those respective years.

The Company is a party to three exclusive license agreements with Antecip Bioventures II LLC, an entity owned by Dr. Tabuteau. See Note 16. License Agreements for further information regarding the license agreements.

Note 20. Segment Information

The Company views its operations and manages its business as one operating and reportable segment, which is the business of developing and delivering novel therapies for the management of CNS disorders. The Company's focus centers around the CNS disorders market as its primary operating environment. Consistent with the operational structure, the Chief Executive Officer, as the chief operating decision maker ("CODM"), manages and allocates resources on a consolidated basis. This decision making process reflects the way in which the financial information is regularly reviewed and used by the CODM to evaluate performance, set operational targets, forecast future financial results, and allocate resources.

The Company's CODM assesses financial performance and allocates resources based on consolidated net loss that also is reported on the consolidated statements of operations. The measure of segment assets is reported on the balance sheet as total consolidated assets. The CODM utilizes consolidated net loss by comparing actual results against budgeted amounts on a quarterly basis. As part of this process, consolidated net loss is a critical performance measure used to evaluate the Company's operating performance and guide strategic decisions and resource allocations, including additional investments in research and development and commercialization activities.

The following table provides information about the Company's one reportable segment and includes the reconciliation to consolidated net loss.

	Year ended December 31,		
	2024	2023	2022
Total revenues	$ 385,693	$ 270,600	$ 50,037
Less:			
Cost of revenue (excluding amortization and depreciation)	33,303	26,065	5,198
Research and development expense (excluding share-based compensation expense):			
Solriamfetol	53,678	18,232	2,834
AXS-05	62,877	34,011	23,949
AXS-07	15,587	8,101	9,061
AXS-12	9,362	10,431	7,091
AXS-14	11,881	7,091	2,330
Other research and development[(a)]	12,274	5,998	4,078
General and administrative expense (excluding share-based compensation expense)	54,204	37,355	25,473
Selling and marketing expense (excluding share-based compensation expense)	293,355	237,228	104,659
Share based compensation expense	85,218	62,620	37,726
Loss in fair value of contingent consideration	28,124	48,918	3,298
Interest expense, net[(b)]	6,569	6,453	7,335
Other segment items[(c)]	6,477	7,335	4,139
Segment net loss	(287,216)	(239,238)	(187,134)
Reconciliation of net loss			
Adjustments and reconciling items	—	—	—
Consolidated net loss	(287,216)	(239,238)	(187,134)

(a) Other research and development expenses primarily consist of facilities charges, third party consultant costs, costs related to other product candidates, and other unallocated costs.

(b) Interest expense, net of $6,569 for the year ended December 31, 2024 comprises (i) consolidated interest expense of $21,581 and (ii) consolidated interest income of $15,012. Interest expense, net of $6,453 for the year ended December 31, 2023 comprises (i) consolidated interest expense of $20,034 and (ii) consolidated interest income of $13,581. Interest expense, net of $7,335 for the year ended December 31, 2022 comprises (i) consolidated interest expense of $9,659 and (ii) consolidated interest income of $2,324.

(c) Other segment items included in Segment net loss includes intangible asset amortization and income tax expense.

See Note 2. Summary of Significant Accounting Policies for further details on the products from which the Company derives its revenues.

See Note 15. Revenues for details of revenue from external customers by geography.

Note 21. Subsequent Events

In January 2025, the Company entered into an amended sublease agreement for its corporate office located at One World Trade Center in New York, New York.

On January 30, 2025, the FDA approved Symbravo (meloxicam and rizatriptan) for the acute treatment of migraine with or without aura in adults.

On February 10, 2025, the Company announced that it had entered into a settlement agreement with Teva to resolve all outstanding litigation between the parties relating to Auvelity. Under the terms of the settlement agreement, the Company will grant Teva a license to sell its generic version of Auvelity beginning on or after March 31, 2039, if pediatric exclusivity is granted for Auvelity, or on or after September 30, 2038, if no pediatric exclusivity is granted, subject to FDA approval and conditions and exceptions customary for agreements of this type.

INDEX OF EXHIBITS

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation of the Company (Incorporated by reference, Exhibit 3.1 to the Company's Current Report on Form 8-K (No. 001-37635) filed November 24, 2015).
3.2	Amended and Restated Bylaws of the Company (Incorporated by reference, Exhibit 3.2 to the Company's Current Report on Form 8-K (No. 001-37635) filed November 24, 2015).
4.1	Specimen Certificate evidencing shares of Company's common stock (Incorporated by reference, Exhibit 4.1 to Amendment No. 1 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 30, 2015).
4.2	Form of warrant to purchase shares of Company's common stock issued in 2013 (Incorporated by reference, Exhibit 4.2 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015).
4.3	Form of warrant to purchase shares of Company's common stock issued in 2014 (Incorporated by reference, Exhibit 4.3 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015).
4.4	Form of Warrant (Incorporated by reference, Exhibit 4.1 to the Company's Current Report on Form 8-K filed December 4, 2017).
4.5	Warrant Agreement, dated as of September 25, 2020, by and between Axsome Therapeutics, Inc. and Hercules Capital, Inc. (Incorporated by reference, Exhibit 10.4 to the Company's Quarterly Report on Form 10-Q, filed November 5, 2020).
4.6	Description of Securities (Incorporated by reference, Exhibit 4.13, to the Company's Annual Report on Form 10-K, filed March 12, 2020).
10.1+	Axsome Therapeutics, Inc. 2013 Equity Compensation Plan and Form of Nonqualified Stock Option Agreement thereunder (Incorporated by reference, Exhibit 10.1 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015).
10.2+	Axsome Therapeutics, Inc. Amended and Restated 2015 Omnibus Incentive Compensation Plan (Incorporated by reference, Exhibit 10.2 to the Company's Annual Report on Form 10-K, filed February 23, 2024).
10.3+	Axsome Therapeutics, Inc. Form of Stock Option Agreement pursuant to the Amended and Restated 2015 Omnibus Incentive Compensation Plan (Incorporated by reference, Exhibit 99.2 to the Company's Registration Statement on Form S-8 (No. 333-208579) filed December 16, 2015).
10.4+	Axsome Therapeutics, Inc. Form of Restricted Stock Unit Agreement (Non-Executives) pursuant to the Amended and Restated 2015 Omnibus Incentive Compensation Plan (Incorporated by reference, Exhibit 99.3 to the Company's Registration Statement on Form S-8 (File No. 333-238174), filed May 11, 2020).
10.5+	Axsome Therapeutics, Inc. Form of Restricted Stock Unit Agreement (Executives and Non-Employee Directors) pursuant to the Amended and Restated 2015 Omnibus Incentive Compensation Plan (Incorporated by reference, Exhibit 99.4 to the Company's Registration Statement on Form S-8 (File No. 333-238174), filed May 11, 2020).
10.6+	Axsome Therapeutics, Inc. 2023 Employee Stock Purchase Plan (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K, filed on June 8, 2023).
10.7++	License Agreement, dated January 12, 2012, by and between the Company and Antecip Bioventures II LLC, as modified by the First Amendment to License Agreement, dated August 21, 2015, by and between the Company and Antecip Bioventures II LLC (Incorporated by reference, Exhibit 10.2 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015).

10.8++	License Agreement, dated June 6, 2012, by and between the Company and Antecip Bioventures II LLC, as modified by the First Amendment to License Agreement, dated August 21, 2015, by and between the Company and Antecip Bioventures II LLC (Incorporated by reference, Exhibit 10.4 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015).
10.9+	Consulting Agreement, dated April 13, 2012, by and between the Company and Mark Coleman, M.D., as modified by the First Amendment to Consulting Agreement, dated June 2, 2014, by and between the Company and Mark Coleman, M.D (Incorporated by reference, Exhibit 10.5 to the Company's Registration Statement on Form S-1 (No. 333-207393) filed October 13, 2015).
10.10	Form of Purchase Agreement, dated as of November 30, 2017 among Axsome Therapeutics, Inc. and the purchasers thereunder (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K filed December 4, 2017).
10.11+	Nick Pizzie Offer Letter, dated April 16, 2018 (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed May 8, 2018).
10.12	Form of Purchase Agreement, dated as of September 27, 2018, by and among the Company and the investors party thereto (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K, filed September 28, 2018).
10.13+++	License Agreement, dated as of January 10, 2020, by and between the Company and Pfizer Inc. (Incorporated by reference, Exhibit 10.15 to the Company's Annual Report on Form 10-K, filed March 12 2020).
10.14	Share Transfer Agreement by and between the Company and Pfizer Inc. (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K, filed January 13, 2020).
10.15	WeWork Membership Agreement effective as of August 1, 2020, by and between the Company and 22 Cortlandt Street HBQ LLC (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, filed August 10, 2020).
10.16+++	Agreement, dated as of September 3, 2020, by and between Axsome Therapeutics, Inc. and David Marek (Incorporated by reference, Exhibit 10.2 to the Company's Amended Quarterly Report on Form 10-Q/A, filed November 6, 2020).
10.17	Loan and Security Agreement, dated as of September 25, 2020, by and among Axsome Therapeutics, Inc., the Lenders who from time to time may be party thereto, and Hercules Capital, Inc., in its capacity as administrative agent and collateral agent for itself and the Lenders (Incorporated by reference, Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q, filed November 5, 2020).
10.18+++	First Amendment to Loan and Security Agreement, dated as of October 14, 2021, by and among Axsome Therapeutics, Inc., the Lenders who from time to time may be party thereto, and Hercules Capital, Inc., in its capacity as administrative agent and collateral agent for itself and the Lenders (Incorporated by reference, Exhibit 10.1, to the Company's Quarterly Report on Form 10-Q, filed on November 8, 2021).
10.19+++	Second Amendment to Loan and Security Agreement, dated as of March 27, 2022, by and among Axsome Therapeutics, Inc., the Lenders who from time to time may be party thereto, and Hercules Capital, Inc., in its capacity as administrative agent and collateral agent for itself and the Lenders (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, filed May 2, 2022).
10.20+++	Third Amendment to Loan and Security Agreement, dated January 9, 2023, by and among Axsome Therapeutics, Inc., the Lenders who from time to time may be party thereto, and Hercules Capital, Inc., in its capacity as administrative agent and collateral agent for itself and the Lenders (Incorporated by reference, Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q, filed May 9, 2023).
10.21	Fourth Amendment to Loan and Security Agreement, dated May 8, 2023, by and among Axsome Therapeutics, Inc., the Lenders who from time to time may be party thereto, and Hercules Capital, Inc., in its capacity as administrative agent and collateral agent for itself and the Lenders (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, filed August 7, 2023).
10.22+++	Fifth Amendment to Hercules Loan and Security Agreement, dated September 30, 2024, by and among Axsome Therapeutics, Inc., the Lenders who from time to time may be party thereto, and Hercules Capital,

	Inc., in its capacity as administrative agent and collateral agent for itself and the Lenders (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, filed November 12, 2024).
10.23	Direct Agreement, by and among Axsome Therapeutics, Inc., Antecip Bioventures II LLC, and Hercules Capital Inc., as collateral agent for itself and the Lenders (Incorporated by reference, Exhibit 10.5 to the Company's Quarterly Report on Form 10-Q, filed November 5, 2020).
10.24+++	Asset Purchase Agreement, dated as of March 25, 2022, between Jazz Pharmaceuticals plc and Axsome Therapeutics, Inc. (Incorporated by reference, Exhibit 10.1 to the Company's Current Report on Form 8-K, filed on March 31, 2022).
10.25	Form of Warrant Agreement, dated as of May 9, 2022, between Axsome Therapeutics, Inc. and Hercules Capital, Inc. (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, filed August 9, 2022).
10.26	Share Transfer Agreement, dated as of May 9, 2022, between Axsome Therapeutics, Inc., Hercules Capital, Inc., Hercules Private Global Venture Growth Fund I L.P. and Hercules Private Credit Fund I L.P. (Incorporated by reference, Exhibit 10.2 to the Company's Quarterly Report on Form 10-Q, filed August 9, 2022).
10.27+++	License Agreement, dated February 21, 2023, by and between Axsome Malta Ltd. and Atnahs Pharma UK Limited (Incorporated by reference, Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q, filed May 9, 2023).
10.28+++	Sublease, dated February 21, 2023, between Advance Magazine Publishers d/b/a Conde Nast and Axsome Therapeutics, Inc. (Incorporated by reference, Exhibit 10.3 to the Company's Quarterly Report on Form 10-Q, filed May 9, 2023).
19.1**	Axsome Therapeutics, Inc. Insider Trading Policy.
21.1**	Subsidiaries of the Company.
23.1**	Consent of Deloitte & Touche LLP.
23.2**	Consent of Ernst & Young LLP.
31.1**	Certification of Principal Executive Officer pursuant to Rule 13a-14(a)/15d-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2**	Certification of Principal Financial Officer pursuant to Rule 13a-14(a)/15d-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1**	Certification of Principal Executive Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (furnished herewith).
32.2**	Certification of Principal Financial Officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 (furnished herewith).
97.1	Axsome Therapeutics, Inc. Dodd-Frank Clawback Policy (Incorporated by reference, Exhibit 97.1 to the Company's Annual Report on Form 10-K, filed February 23, 2024).
101.INS	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document).
101.SCH	Inline XBRL Taxonomy Extension Schema With Embedded Linkbase Documents.
104	Cover Page Interactive Data File (formatted as inline XBRL with applicable taxonomy extension information contained in Exhibits 101.).

\+ Indicates management contract or compensatory plan.

++ Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the U.S. Securities and Exchange Commission.

+++ Certain portions of this exhibit have been redacted pursuant to Item 601(b)(10)(iv) of Regulation S-K.

** Filed herewith.

ITEM 16. FORM 10-K SUMMARY

We may voluntarily include a summary of information required by Form 10-K under this Item 16. We have elected not to include such summary information.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, on this 18th day of February 2025.

AXSOME THERAPEUTICS, INC.

By /s/ Herriot Tabuteau, M.D.
Herriot Tabuteau, M.D.
Chief Executive Officer

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

Signature	Title	Date
/s/ Herriot Tabuteau, M.D. Herriot Tabuteau, M.D.	Chief Executive Officer and Chairman of the Board (Principal Executive Officer)	February 18, 2025
/s/ Nick Pizzie Nick Pizzie	Chief Financial Officer (Principal Financial and Accounting Officer)	February 18, 2025
/s/ Roger Jeffs, Ph.D. Roger Jeffs, Ph.D.	Director	February 18, 2025
/s/ Mark Coleman, M.D. Mark Coleman, M.D.	Director	February 18, 2025
/s/ Mark Saad Mark Saad	Director	February 18, 2025
/s/ Susan Mahony, Ph.D., M.B.A. Susan Mahony, Ph.D., M.B.A.	Director	February 18, 2025

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Board of Directors
Herriot Tabuteau, M.D.
Chief Executive Officer and Chairman of the Board
Axsome Therapeutics, Inc.

Mark Coleman, M.D.[1] [2] [3]
Medical Director, Pikesville Office
National Spine and Pain Centers, LLC

Roger Jeffs, Ph.D.[1] [2] [3]
Chief Executive Officer
Liquidia Corporation

Mark Saad[1] [2] [3]
Chief Executive Officer
NuLids, LLC

Susan Mahony, Ph.D., M.B.A.[1] [2] [3]
Former President
Lilly Oncology

Standing Committees of the Board of Directors
(1) Compensation Committee
(2) Audit Committee
(3) Nominating and Corporate Governance Committee

Executive Officers
Herriot Tabuteau, M.D.
Chief Executive Officer

Nick Pizzie, C.P.A., M.B.A.
Chief Financial Officer

Mark Jacobson, M.A.
Chief Operating Officer

Hunter Murdock, Esq.
General Counsel

Ari Maizel, M.B.A.
Chief Commercial Officer

Corporate Headquarters
Axsome Therapeutics, Inc.
One World Trade Center, 29th Floor
New York, New York 10007
Phone: (212) 332-3241
Fax: (212) 320-0245
Website: http://www.axsome.com

Transfer Agent and Registrar
Equiniti Trust Company, LLC
6201 15th Avenue
Brooklyn, New York 11219

Counsel
DLA Piper LLP (US)
1251 Avenue of the Americas, 27th Floor
New York, New York 10020-1104

Independent Registered Public Accounting Firm
Deloitte & Touche LLP
30 Rockefeller Plaza, 41st Floor
New York, New York 10112

Number of Holders of Common Stock
As of April 14, 2025 there are 2 stockholders of record of Common Stock.

Dividends
The Company has not paid any cash dividends on its Common Stock since its inception and does not anticipate paying any such cash dividends in the foreseeable future.

Market for Common Stock
Nasdaq Global Market
Symbol: AXSM

SEC Form 10-K and Stockholders' Inquiries
A copy of the Company's Annual Report to the Securities and Exchange Commission on Form 10-K is available without charge. Requests for Form 10-K or other stockholder inquiries should be directed in writing to:

Investor Relations
Axsome Therapeutics, Inc.
One World Trade Center, 29th Floor
New York, New York 10007

Annual Meeting
The Annual Meeting of Stockholders will take place on Friday, June 6, 2025 at 9:00 a.m. via live webcast at www.virtualshareholdermeeting.com/AXSM2025