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

Form 10-K

(Mark One)

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

For the fiscal year ended December 31, 2021

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: 000-50768

ACADIA PHARMACEUTICALS INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware **(State or Other Jurisdiction of Incorporation or Organization)**	**06-1376651** **(I.R.S. Employer Identification Number)**
12830 El Camino Real, Suite 400 **San Diego, California** **(Address of Principal Executive Offices)**	**92130** **(Zip Code)**

Registrant's telephone number, including area code:

(858) 558-2871

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	**ACAD**	**The Nasdaq Stock Market LLC**

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 15(d) of the Securities Exchange Act of 1934. 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 (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, 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 Securities Exchange Act of 1934:

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐
		Emerging growth company	☐

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

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

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes ☐ No ☒

As of June 30, 2021, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common stock held by non-affiliates of the registrant was approximately $2.5 billion, based on the closing price of the registrant's common stock on the Nasdaq Global Select Market on June 30, 2021 of $24.39 per share.

As of February 15, 2022, 161,203,748 shares of the registrant's common stock, $0.0001 par value, were outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement to be filed with the Securities and Exchange Commission by April 30, 2022 are incorporated by reference into Part III of this report.

ACADIA PHARMACEUTICALS INC.

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PART I

FORWARD-LOOKING STATEMENTS

This report and the information incorporated herein by reference contain forward-looking statements that involve a number of risks and uncertainties, as well as assumptions that, if they never materialize or prove incorrect, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements can only be based on facts and factors currently known by us. Consequently, forward-looking statements are inherently subject to risks and uncertainties, and actual results and outcomes may differ materially from results and outcomes discussed in the forward-looking statements. In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and you are cautioned not to unduly rely upon these statements.

Forward-looking statements can be identified by the use of forward-looking words such as "believes," "expects," "hopes," "may," "will," "plans," "intends," "estimates," "could," "should," "would," "continue," "seeks," "aims," "projects," "predicts," "pro forma," "anticipates," "potential" or other similar words (including their use in the negative), or by discussions of future matters such as the benefits to be derived from NUPLAZID® (pimavanserin), trofinetide and from our drug candidates, the potential market opportunities for pimavanserin and our drug candidates, our strategy for the commercialization of NUPLAZID, our plans for exploring and developing pimavanserin for indications other than Parkinson's disease psychosis, our plans and timing with respect to seeking regulatory approvals, the potential commercialization of any of our drug candidates that receive regulatory approval, the progress, timing, results or implications of clinical trials and other development activities involving pimavanserin and our drug candidates, our strategy for discovering, developing and, if approved, commercializing drug candidates, our existing and potential future collaborations, our estimates of future payments, revenues and profitability, our estimates regarding our capital requirements, future expenses and need for additional financing, possible changes in legislation, and other statements that are not historical. These statements include but are not limited to statements under the captions "Business," "Risk Factors," and "Management's Discussion and Analysis of Financial Condition and Results of Operations" as well as other sections in this report. You should be aware that the occurrence of any of the events discussed under the caption "Risk Factors" and elsewhere in this report could substantially harm our business, results of operations and financial condition and cause our results to differ materially from those expressed or implied by our forward-looking statements. If any of these events occurs, the trading price of our common stock could decline and you could lose all or a part of the value of your shares of our common stock.

The cautionary statements made in this report are intended to be applicable to all related forward-looking statements wherever they may appear in this report. We urge you not to place undue reliance on these forward-looking statements, which speak only as of the date of this report.

Item 1. *Business.*

Company Overview

We are a biopharmaceutical company focused on the development and commercialization of innovative medicines that address unmet medical needs in central nervous system (CNS) disorders. We have a portfolio of product opportunities led by our novel drug, NUPLAZID (pimavanserin), which was approved by the U.S. Food and Drug Administration (FDA) in April 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP), and is the first and only drug approved in the United States for this condition. NUPLAZID is a selective serotonin inverse agonist/antagonist, preferentially targeting 5-HT_{2A} receptors with no appreciable affinity for dopaminergic, histaminergic, or muscarinic receptors. Through this novel mechanism, NUPLAZID demonstrated significant efficacy in reducing the hallucinations and delusions associated with PDP without negatively impacting motor function in our Phase 3 pivotal trial. NUPLAZID has the potential to avoid many of the debilitating side effects of existing antipsychotics, none of which are approved by the FDA for the treatment of PDP. We hold worldwide commercialization rights to pimavanserin.

We believe that pimavanserin has the potential to address important unmet medical needs in neurological and psychiatric disorders in addition to PDP and we plan to continue to study the use of pimavanserin in multiple disease states. Beyond PDP, we believe Alzheimer's disease psychosis (ADP), represents one of our most important opportunities for further development. In February 2022, we resubmitted to the FDA a supplemental New Drug Application (sNDA) for NUPLAZID for the treatment of hallucinations and delusions associated with ADP.

Negative symptoms of schizophrenia have been associated with poor long-term outcomes and disability even when the positive symptoms are well controlled, representing a high unmet need. There are currently no FDA-approved therapies for the treatment of the negative symptoms of schizophrenia. We are currently exploring the utility of pimavanserin in this area. In the fourth quarter of 2019 we announced positive results from our pivotal ADVANCE study and in the third quarter of 2020, we initiated a second pivotal study, ADVANCE-2. The Phase 3 program is evaluating the efficacy of pimavanserin in patients with predominantly negative symptoms of schizophrenia who have achieved adequate control of positive symptoms with their existing antipsychotic treatment. We anticipate announcing top-line results from the Phase 3 ADVANCE-2 study in 2023.

In August 2018, we acquired an exclusive North American license to develop and commercialize trofinetide for Rett syndrome and other indications from Neuren Pharmaceuticals Limited (Neuren). Rett syndrome is a debilitating neurological disorder that occurs predominantly in females following apparently normal development for the first six months of life. Typically, between six to eighteen months of age, patients experience a period of rapid decline with loss of purposeful hand use and spoken communication and inability to independently conduct activities of daily living. Symptoms also include seizures, disorganized breathing patterns, scoliosis and sleep disturbances. Currently, there are no approved medicines for the treatment of Rett syndrome. In December 2021, we announced positive results from our pivotal Phase 3 LAVENDER study. The study demonstrated a statistically significant improvement over placebo for both co-primary endpoints as well as key secondary endpoint. We plan to submit to the FDA a New Drug Application (NDA) for trofinetide for the treatment of Rett syndrome around mid-year 2022.

In March 2020, we acquired an exclusive worldwide license from Vanderbilt University to develop and commercialize novel drug candidates targeting positive allosteric modulators (PAMs) of the muscarinic M1 receptor with the potential to treat cognition in dementia and psychotic symptoms in schizophrenia. These M1 PAMs represent a promising approach for improving cognitive function and other neuropsychiatric symptoms in patients suffering from CNS disorders. The license covers a portfolio of candidates, with molecules at various stages of testing, including the lead compound, ACP-319, which is in Phase 1 testing, and several additional compounds in preclinical development as well as any additional compounds generated in an ongoing discovery program.

In August 2020, we acquired CerSci Therapeutics Incorporated (CerSci). The lead product candidate, ACP-044, is a non-opioid, redox modulator in development for treatment of acute and chronic pain. The mechanism of action is believed to modulate redox pathways involved in pain signaling by removing increased levels of reactive oxygen and nitrogen species caused by tissue injury, inflammation, and disease. In addition, through the acquisition, we obtained a portfolio of preclinical stage molecules, including brain penetrant compounds, with potential for symptomatic and disease modifying utility in neurodegenerative diseases. ACP-044 has shown promising results in animal models evaluating incisional, inflammatory, and neuropathic pain, as well as favorable tolerability and pharmacokinetic properties in Phase 1 trials. In March 2021, we initiated a Phase 2 study evaluating ACP-044 for the treatment of postoperative pain following bunionectomy surgery. We anticipate results from this study around the end of the first quarter of 2022. In June 2021, we initiated an additional Phase 2 study evaluating ACP-044 for the treatment of pain associated with osteoarthritis and currently anticipate announcing top-line results around the end of 2022.

In January 2022, we entered into a license and collaboration agreement with Stoke Therapeutics, Inc. (Stoke) to discover, develop and commercialize novel RNA-based medicines for the potential treatment of severe and rare genetic neurodevelopmental diseases of the CNS. The collaboration includes SYNGAP1 syndrome, Rett syndrome (MECP2), and an undisclosed neurodevelopmental target. For the SYNGAP1 program, the two companies will jointly share global research, development and commercialization responsibilities and share 50/50 in all worldwide costs and future profits. For the Rett syndrome (MECP2) and the undisclosed neurodevelopmental program, Stoke will lead research and pre-clinical development activities, while we will lead clinical development and commercialization activities.

Corporate Information

We were originally incorporated in Vermont in 1993 as Receptor Technologies, Inc. We reincorporated in Delaware in 1997 and our headquarters are in San Diego, California. We maintain a website at *www.acadia-pharm.com*, to which we regularly post copies of our press releases as well as additional information about us. Our filings with the Securities and Exchange Commission (SEC), are available free of charge through our website as soon as reasonably practicable after being electronically filed with or furnished to the SEC. Interested persons can subscribe on our website to email alerts that are sent automatically when we issue press releases, file our reports with the SEC or post certain other information to our website. Information contained in our website does not constitute a part of this report or our other filings with the SEC.

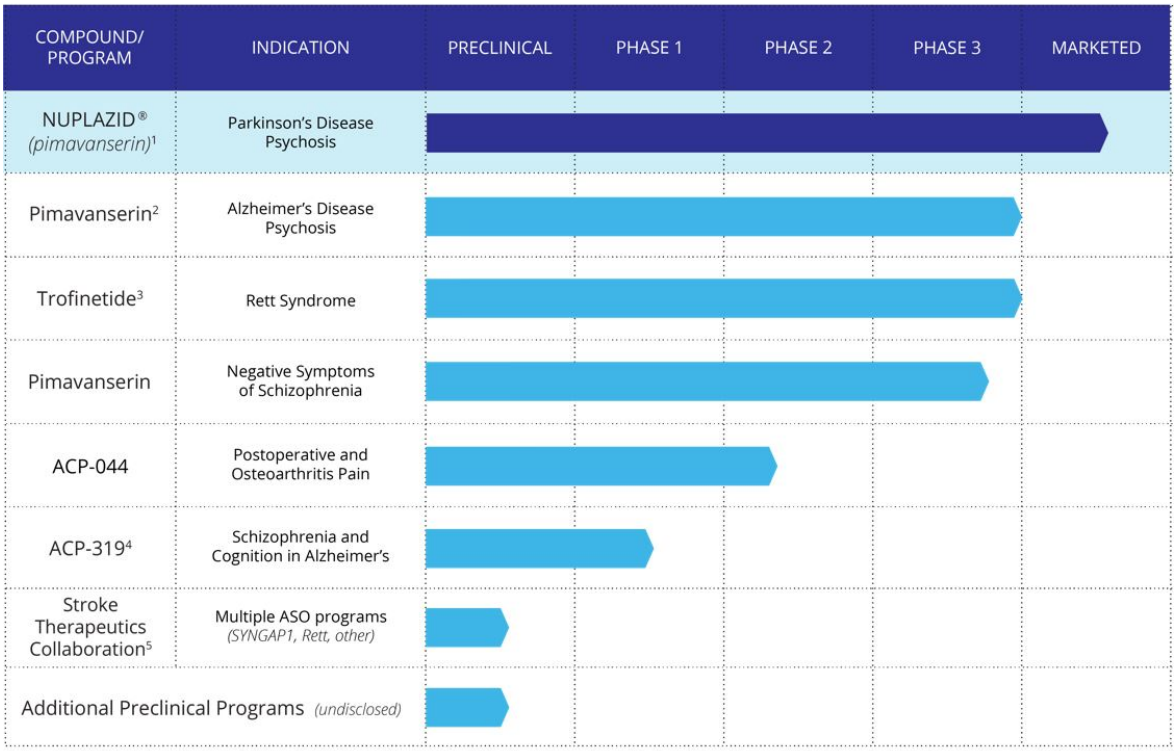
We own or have rights to various trademarks, copyrights and trade names used in our business, including Acadia® and NUPLAZID®. Our logos and trademarks are the property of Acadia Pharmaceuticals Inc. All other brand names or trademarks appearing in this report are the property of their respective holders. Use or display by us of other parties' trademarks, trade dress, or products in this report is not intended to, and does not, imply a relationship with, or endorsement or sponsorship of us, by the trademark or trade dress owners.

Our Strategy

Our strategy is to identify, develop and commercialize innovative therapies that address unmet medical needs in CNS disorders and rare diseases. Key elements of our strategy are to:

- ***Drive the successful commercialization of NUPLAZID for Parkinson's disease psychosis in the United States.*** NUPLAZID was approved by the FDA in April 2016 for the treatment of hallucinations and delusions associated with PDP. We launched NUPLAZID in the United States in May 2016 and an important objective is to establish NUPLAZID as the standard of care for PDP. We employ U.S. sales specialists that are focused on promoting NUPLAZID to physicians who treat PDP patients, including neurologists, psychiatrists and long-term care physicians.
- ***Advance our late-stage opportunities in Alzheimer's disease psychosis, Rett syndrome and negative symptoms of schizophrenia.*** In February 2022, we resubmitted to the FDA an sNDA for NUPLAZID for the treatment of hallucinations and delusions associated with ADP. In addition, based on the positive results from the Phase 3 LAVENDER study, we plan to submit to the FDA an NDA for trofinetide for the treatment of Rett syndrome around mid-year 2022. We also have an ongoing Phase 3 program evaluating pimavanserin for the treatment of negative symptoms of schizophrenia with top-line results expected in 2023.
- ***Develop our next wave of breakthroughs.*** We are advancing multiple clinical programs focused on the treatment of neurological and psychiatric indications that are underserved due to limited or no treatment options and represent large unmet medical needs. We have ongoing research programs and are focused on licensing and acquiring new programs through strategic business development, such as recent transaction with Stoke.

Our Pipeline



[1]NUPLAZID (pimavanserin) is only approved in the U.S. by the FDA for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis.

[2]Acadia received a CRL for its sNDA for pimavanserin for the treatment of DRP. Acadia has resubmitted the sNDA for the treatment of hallucinations and delusions associated with Alzheimer's disease psychosis.

[3]Acadia has an exclusive license to develop and commercialize trofinetide in North America from Neuren Pharmaceuticals.

[4]Acadia has an exclusive worldwide license to develop and commercialize ACP-319 and other M1 PAM program compounds from Vanderbilt University.

[5]Acadia entered into a collaboration with Stoke Therapeutics to discover, develop and commercialize novel RNA-based medicines for the potential treatment of severe and rare genetic neurodevelopmental diseases.

NUPLAZID (pimavanserin)

Pimavanserin is a new chemical entity that we discovered and that was approved by the FDA in April 2016 for the treatment of hallucinations and delusions associated with PDP. It is the only drug approved in the United States for this condition and is marketed under the tradename NUPLAZID in the United States. NUPLAZID is a selective serotonin inverse agonist/antagonist preferentially targeting the 5-HT_{2A} receptor, a key serotonin receptor that plays an important role in psychosis. Through this novel mechanism, NUPLAZID demonstrated significant efficacy in reducing the hallucinations and delusions associated with PDP without negatively impacting motor function in our Phase 3 pivotal trial. NUPLAZID has the potential to avoid many of the debilitating side effects of existing antipsychotics, none of which are approved by the FDA in the treatment of PDP. We hold worldwide commercialization rights to NUPLAZID for all indications and have established a broad patent portfolio, which includes numerous issued patents in the United States, Europe, and several additional countries. NUPLAZID is available in 34 mg capsule and 10 mg tablet dosage forms.

NUPLAZID as a Treatment for Parkinson's Disease Psychosis

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. According to the Parkinson's Disease Foundation, about one million people in the United States and more than 10 million people globally suffer from this disease. Approximately 50% of Parkinson's patients will experience psychosis over the course of their disease. Parkinson's disease is more common in people over 60 years of age and the prevalence of this disease is expected to increase significantly as the population ages.

PDP is a debilitating disorder commonly characterized by visual hallucinations and delusions that afflicts about 40% of the one million Parkinson's disease patients in the United States. The development of psychosis in patients with Parkinson's disease substantially contributes to the burden of Parkinson's disease and deeply affects their quality of life. PDP is associated with a diminished quality of life, nursing home placement, and increased caregiver stress and burden.

As the first and only drug approved by the FDA for the treatment of hallucinations and delusions associated with PDP, NUPLAZID provides an innovative approach to the treatment of PDP without compromising motor control and potentially avoiding many of the debilitating side effects of existing antipsychotics.

In connection with the FDA approval of NUPLAZID, we have agreed to four post-marketing commitments. Three of the four commitments have been fulfilled within the agreed upon timelines. The forth commitments, a randomized, placebo-controlled eight-week study or studies in predominantly frail and elderly patients that would add to the NUPLAZID safety database by exposing an aggregate of at least 500 patients to NUPLAZID, remains ongoing.

Pimavanserin as a Treatment for Alzheimer's Disease Psychosis

An estimated over 6.0 million people in the United States are living with Alzheimer's disease dementia and studies suggest that approximately 30% of patients, or 1.8 million people, have psychosis, commonly consisting of delusions and hallucinations. Approximately 900 thousand patients in the United States are currently treated for ADP and of those treated, approximately two-thirds are treated with off-label anti-psychotics.

Symptoms of ADP are often persistent and may occur with increasing frequency with progression of disease as patients become more impaired. Serious consequences have been associated with persistent or severe psychosis in persons with dementia such as repeated hospital admissions, earlier progression to nursing home care, severe dementia, and death. There are currently no FDA-approved treatments for ADP. Off-label use of typical and atypical antipsychotics is associated with modest and often equivocal efficacy in these patients. In addition, use of currently available antipsychotics is associated with a significant acceleration in cognitive decline in patients with dementia as well as numerous off-target toxicities, thus negatively impacting the primary illness. The cognitive effects of treatment with an atypical antipsychotic were evaluated in the National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD) study. In this study, patients on any atypical antipsychotic had significantly greater rates of decline in cognitive function compared to patients on placebo. This pronounced negative impact of currently used antipsychotics on cognitive function is believed to be associated with the common pharmacologic property of these drugs, namely blocking of dopamine receptors. Atypical antipsychotics are associated with a number of off-target and dose-limiting side effects, such as extrapyramidal symptoms, orthostatic hypotension, hematologic abnormalities, and metabolic, gastrointestinal and sedative effects. These off-target toxicities are associated with increased risk for falls, infection, aspiration pneumonia, and other serious complications in this vulnerable patient population. With no approved therapies for the treatment of patients with ADP and current off-label use of atypical antipsychotics carrying significant morbidity risks including worsening in cognitive decline and other off target toxicities, we believe that ADP represents an area of high unmet need.

In September 2017, we initiated HARMONY, a Phase 3, randomized, double-blind, placebo-controlled relapse prevention study, evaluating the efficacy and safety of pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis (DRP), including a subgroup of ADP patients. The objective of the study was to evaluate the ability of pimavanserin to prevent relapse of psychosis in a broad population of patients with the most common subgroups of dementia. Furthermore, in the fourth quarter of 2017, the FDA granted Breakthrough Therapy Designation to pimavanserin for the treatment of DRP.

The HARMONY study included a 12-week open-label stabilization period during which 392 patients with DRP were treated with pimavanserin 34 mg once daily. Dose reduction to 20 mg once daily was allowed based on tolerability within the first four weeks. Following the 12-week open-label period, patients who met pre-specified criteria for treatment response at both weeks 8 and weeks 12 were then randomized into the double-blind period of the study to continue their pimavanserin dose (34 mg or 20 mg per day) or switched to placebo and followed for up to 26 weeks or until a relapse of psychosis occurred. The primary endpoint in the study was time to relapse in the double-blind period as represented by the Kaplan-Meier curve and the hazard ratio.

In September 2019, we announced that our Phase 3 HARMONY relapse prevention trial evaluating pimavanserin for the treatment of DRP would be stopped early for positive efficacy as it met the primary endpoint, demonstrating a highly statistically significant longer time to relapse of psychosis with pimavanserin compared to placebo in a planned interim efficacy analysis. In December 2019, we announced top-line results from the HARMONY study in a presentation at the 12th CTAD Meeting. Pimavanserin met the primary endpoint of the study by significantly reducing the risk of relapse of psychosis by 2.8 fold compared to placebo (HR = 0.353; one-sided p=0.0023). In addition, pimavanserin met the key secondary endpoint by significantly reducing risk of discontinuation for any reason by 2.2 fold (HR = 0.452; one-sided p=0.0024). Clinically meaningful effect was also observed in the pre-specified ADP subgroup of 123 patients during the double-blind portion of the study (HR = 0.62). In the 12-week open-label treatment period, 61.8% of eligible patients met pre-specified criteria for pimavanserin treatment response at both week 8 and week 12 and were subsequently randomized into the double-blind period of the study. In an exploratory analysis in the open label-phase, the mean percent reduction from baseline on the SAPS+HD was 46.9%, 63.0% and 75.2%, at Weeks 4, 8 and enriched Week 12 population, respectively.

Pimavanserin was well-tolerated over the entire nine-month study duration. Patients receiving pimavanserin treatment had no worsening in cognition, as measured by the MMSE score, from baseline and no worsening of motor symptoms, as measured by the ESRS-A, from baseline. In the double-blind period, adverse events were observed in 41.0% of patients on pimavanserin and 36.6% of patients on placebo. Discontinuations due to adverse events were 2.9% for pimavanserin and 3.6% for placebo. Serious adverse events were 4.8% in the pimavanserin group and 3.6% in the placebo group. One death was reported in the open-label period and one death was reported in the pimavanserin group during the double-blind period. Investigators determined neither death was related to the study drug. Additionally, pimavanserin did not result in clinically significant differences in vital signs, weight, or daytime sedation compared to placebo.

In July 2020 the FDA notified us of their filing of our sNDA with a PDUFA target action date of April 3, 2021. The sNDA was supported by results from the pivotal Phase 3 HARMONY study and included positive efficacy results from two additional placebo-controlled studies, both of which met their respective primary endpoints: the Phase 2 (-019) study in patients with Alzheimer's disease psychosis and the Phase 3 (-020) study in patients with PDP. The sNDA included a large safety database from completed and ongoing studies representing over 1,500 patients with neurodegenerative disease.

In April 2021 the FDA issued a complete response letter (CRL) indicating that it had completed its review of the sNDA and determined that the application could not be approved in its present form. In the CRL, the FDA cited a lack of statistical significance in some of the subgroups of dementia in the HARMONY study, as well as insufficient numbers of patients with certain less common dementia subgroups as lack of substantial evidence of effectiveness to support approval. The FDA also stated in the CRL that it considers Alzheimer's disease psychosis study -019 to not be adequate and well controlled, citing that it was a single center study with no type I error control of secondary endpoints in which certain protocol deviations occurred. An end of review (Type A) meeting was held in June 2021, at which the FDA reiterated, as stated in the CRL, that pimavanserin should be studied by individual subgroups of DRP, and advised us that the best path forward may be to conduct an additional clinical study in each of the subgroups for which we would seek approval. However, the FDA was also open to reviewing additional analyses from the HARMONY and -019 studies in support of a potential resubmission for individual subgroups without additional clinical studies. We subsequently held additional meetings (Type B) with the FDA and further discussed the potential for a resubmission based on additional analyses supporting a potential indication for treatment of ADP specifically. In February 2022, we made a resubmission to the FDA for NUPLAZID for the treatment of hallucinations and delusions associated with ADP and to provide a complete response to the issues outlined in FDA's CRL.

Pimavanserin as a Treatment for the Negative Symptoms of Schizophrenia

Schizophrenia is a severe chronic mental illness that involves disturbances in cognition, perception, emotion, and other aspects of behavior. These disturbances may include positive symptoms, such as hallucinations and delusions, and a range of negative symptoms, including loss of interest and emotional withdrawal. Schizophrenia is associated with persistent impairment of a patient's social functioning and productivity. Cognitive disturbances often prevent patients with schizophrenia from readjusting to society. As a result, patients with schizophrenia are normally required to be under medical care for their entire lives. According to the National Institute of Mental Health (NIMH), approximately 1% of the U.S. population suffers from schizophrenia.

Most patients with schizophrenia in the United States today are treated with second-generation, or atypical, antipsychotics, which induce fewer motor disturbances than typical, or first-generation, antipsychotics, but still fail to fully address some of the negative symptoms of schizophrenia for a significant portion of patients. In addition, currently prescribed treatments have either negligible effects on cognitive symptoms of schizophrenia or may even further impair cognitive performance. It is believed that the efficacy of atypical antipsychotics is due to their interactions with dopamine and 5-HT_{2A} receptors. Despite their commercial success, current antipsychotic drugs have substantial limitations, including inadequate efficacy and severe side effects. The side effects associated with these atypical agents may include weight gain, type 2 diabetes, metabolic, sexual and cardiovascular side effects, movement disturbances or sedation.

In November 2016, we announced that we initiated ADVANCE, a Phase 2 study to evaluate pimavanserin for adjunctive treatment in patients with negative symptoms of schizophrenia. Studies show that about 40% to 50% of schizophrenia patients suffer from prominent negative symptoms. While currently available antipsychotic treatments for schizophrenia mainly target positive symptoms, many patients remain functionally impaired because of residual negative and cognitive symptoms that are harder to treat with atypical antipsychotics. The residual negative and cognitive symptoms limit social functioning. There is currently no drug approved by the FDA for the treatment of the negative symptoms of schizophrenia.

ADVANCE was a Phase 2, 26-week, randomized, double-blind, placebo-controlled, multi-center, international study designed to examine the efficacy and safety of pimavanserin in patients with schizophrenia who have predominant negative symptoms while on a stable background antipsychotic therapy. 403 patients were randomized to receive once-daily pimavanserin (n=201) or placebo (n=202) as an adjunct treatment to their ongoing antipsychotic in a flexible dosing regimen. The starting daily dose of 20 mg of pimavanserin at baseline could have been adjusted to 34 mg or 10 mg during the first eight weeks of treatment. 53.8% of patients who were randomized to receive pimavanserin completed the trial on 34 mg, 44.7% on 20 mg, and 1.5% on 10 mg. The primary endpoint of the study was the change from baseline to week 26 on the NSA-16 total score. In November 2019, we announced positive top-line results from the ADVANCE study. In this study, pimavanserin demonstrated a statistically significant improvement on the study's primary endpoint, the change from baseline to week 26 on the Negative Symptom Assessment-16 (NSA-16) total score, compared to placebo (p=0.043). A greater improvement in the NSA-16 total score compared to placebo was observed in patients who received the highest pimavanserin dose of 34 mg (n=107; unadjusted p=0.0065). Pimavanserin did not separate from placebo on the key secondary endpoint, the Personal and Social Performance (PSP) scale. In the third quarter of 2020, we initiated a second pivotal study, ADVANCE-2. The Phase 3 study will evaluate the efficacy of pimavanserin 34 mg once daily compared to placebo in approximately 386 patients with predominantly negative symptoms of schizophrenia who have achieved adequate control of positive symptoms with their existing antipsychotic treatment. We anticipate announcing top-line results from the Phase 3 ADVANCE-2 study in 2023.

Trofinetide

Trofinetide is a novel synthetic analog of the amino-terminal tripeptide of insulin-like growth factor 1 (IGF-1) designed to treat the core symptoms of Rett syndrome by reducing neuroinflammation and supporting synaptic function. Trofinetide has been granted FDA Fast Track Status and Orphan Drug Designation in the U.S. and Orphan Designation in Europe.

Trofinetide as a Treatment for Rett Syndrome

Rett syndrome is a debilitating neurological disorder that occurs primarily in females following apparently normal development for the first six months of life. Rett syndrome has been most often misdiagnosed as autism, cerebral palsy, or non-specific developmental delay. Rett syndrome is caused by mutations on the X chromosome on a gene called MECP2. There are more than 200 different mutations found on the MECP2 gene that interfere with its ability to generate a normal gene product. Rett syndrome occurs worldwide in approximately one of every 10,000 to 15,000 female births causing problems in brain function that are responsible for cognitive, sensory, emotional, motor and autonomic function. Typically, between six to eighteen months of age, patients experience a period of rapid decline with loss of purposeful hand use and spoken communication and inability to independently conduct activities of daily living. Symptoms also include seizures, disorganized breathing patterns, an abnormal side-to-side curvature of the spine (scoliosis) and sleep disturbances. Currently, there are no approved medicines approved for the treatment of Rett syndrome.

In October 2019, we initiated the Phase 3 LAVENDER study, a randomized, double-blind placebo-controlled study evaluating trofinetide in approximately 180 girls and young women 5 to 20 years of age with Rett syndrome. Half of study participants will receive trofinetide and half will receive placebo. Co-primary efficacy endpoints of the study will measure symptom improvement using the Rett Syndrome Behavior Questionnaire (RSBQ), a caregiver assessment, and the Clinical Global Impression Scale-Improvement (CGI-I), a clinician assessment. In December 2021, we announced positive top-line results from the study. The placebo-controlled study demonstrated a statistically significant improvement over placebo for both endpoints. On the RSBQ, change from baseline to week 12 was -5.1 vs. -1.7 (p=0.0175; effect size=0.37). The CGI-I score at week 12 was 3.5 vs. 3.8 (p=0.0030; effect size=0.47). Additionally, trofinetide demonstrated a statistically significant separation over placebo on the key secondary endpoint, the Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist–Social composite score (CSBS-DP-IT–Social) change from baseline to week 12 was -0.1 vs. -1.1 (p=0.0064; effect size=0.43).

Study treatment discontinuation rates related to treatment emergent adverse events (TEAEs) were 17.2% in the trofinetide group as compared to 2.1% in the placebo group. The most common adverse events were diarrhea (80.6% with trofinetide vs. 19.1% with placebo), of which 97.3% in the trofinetide arm were characterized as mild-to-moderate, and vomiting (26.9% with trofinetide vs. 9.6% with placebo), of which 96% in the trofinetide arm were characterized as mild-to-moderate. Serious adverse events were observed in 3.2% of study participants in both the trofinetide and placebo groups. Patients completing the LAVENDER study had the opportunity to continue to receive trofinetide in the open-label LILAC and LILAC-2 extension studies. More than 95% of participants who completed the LAVENDER study elected to roll-over to the LILAC open-label extension study.

We plan to submit an NDA around mid-year 2022. Trofinetide has been granted Fast Track Status and Orphan Drug Designation for Rett syndrome. Trofinetide has also been granted Rare Pediatric Disease (RPD) designation by the FDA. An NDA with Fast Track and/or Orphan Drug Designation is eligible for priority review. With an RPD we would expect to be awarded a RPD Priority Review Voucher if approved, subject to final determination by the FDA.

ACP-044

ACP-044, is a non-opioid, redox modulator in development for treatment of acute and chronic pain. The mechanism of action is believed to modulate redox pathways involved in pain signaling by removing increased levels of reactive oxygen and nitrogen species caused by tissue injury, inflammation, and disease. There is a significant high unmet need for more effective, safe, non-opioid and non-addictive treatments for pain management. ACP-044 has shown promising results in animal models evaluating incisional, inflammatory, and neuropathic pain, as well as favorable tolerability and pharmacokinetic properties in Phase 1 trials. In March 2021, we initiated a Phase 2 study evaluating ACP-044 for the treatment of postoperative pain following bunionectomy surgery. We anticipate results from this study around the end of the first quarter of 2022. In June 2021, we initiated an additional Phase 2 study evaluating ACP-044 for the treatment of pain associated with osteoarthritis and expect top-line results around year-end 2022.

ACP-319

ACP-319 is a positive allosteric modulator of the muscarinic receptor targeting M1 (M1 PAM). The challenge with targeting the muscarinic system has been issues related to tolerability. Targeting of these receptors has been associated with cholinergic side effects. However, the allosteric modulation of the M1 receptor may achieve the potential therapeutic benefits without the unwanted side effects. Animal studies have demonstrated improvement in models of both cognition and schizophrenia without the cholinergic side effects. Given the high unmet need, ACP-319 is being developed for potential utility in cognition in dementia and psychotic symptoms in schizophrenia. ACP-319 is currently in Phase 1 clinical development.

Competition

We face, and will continue to face, intense competition from pharmaceutical and biotechnology companies, as well as numerous academic and research institutions and governmental agencies, both in the United States and abroad. We compete, or will compete, with existing and new products being developed by our competitors. Some of these competitors are pursuing the development of pharmaceuticals that target the same diseases and conditions that our research and development programs target.

For example, the use of NUPLAZID for the treatment of PDP competes with off-label use of various antipsychotic drugs, including the generic drugs quetiapine, clozapine, risperidone, aripiprazole, and olanzapine.

If approved, pimavanserin for the treatment of ADP would also compete with off-label use of various antipsychotic drugs, including the generic drugs quetiapine, clozapine, risperidone, aripiprazole, and olanzapine, as well as generic mood stabilizers such as valproate. Other generic agents for the treatment of underlying dementia such as donepezil and memantine may also be secondarily used for the treatment of ADP, although NUPLAZID would not be promoted to replace these agents.

Pimavanserin for the treatment of negative symptoms of schizophrenia, if approved for that indication, would compete with off-label use of Vraylar, marketed by Allergan, Rexulti, marketed by Otsuka Pharmaceutical Co., Ltd., Latuda, marketed by Sunovion Pharmaceuticals Inc., Caplyta, marketed by IntraCellular Therapeutics and various generic drugs, including quetiapine, clozapine, risperidone, aripiprazole, and olanzapine.

Trofinetide, if approved, would compete indirectly with off-label usage of branded and generic prescription medications targeted at individual symptoms of Rett syndrome, including antiepileptics, antipsychotics, antidepressants and benzodiazepines. Several academic institutions and pharmaceutical companies are currently conducting clinical trials for the treatment of various symptoms of Rett syndrome.

Other competitors may have a variety of drugs in development or awaiting FDA approval that could reach the market and become established before we have a product to sell for the applicable disorder. Our competitors may also develop alternative therapies that could further limit the market for any drugs that we may develop. Many of our competitors are using technologies or methods different or similar to ours to identify and validate drug targets and to discover novel small molecule drugs. Many of our competitors and their collaborators have significantly greater experience than we do in the following:

- preclinical studies and clinical trials of potential pharmaceutical products;
- obtaining FDA and other regulatory approvals; and
- commercializing pharmaceutical products.

In addition, many of our competitors and their collaborators have substantially greater advantages in the following areas:

- capital resources;
- research and development resources;
- manufacturing capabilities;
- sales and marketing; and
- production facilities.

Smaller companies also may prove to be significant competitors, particularly through proprietary research discoveries and collaborative arrangements with large pharmaceutical and established biotechnology companies. Many of our competitors have products that have been approved or are in advanced development and may develop superior technologies or methods to identify and validate drug targets and to discover novel small molecule drugs. We face competition from other companies, academic institutions, governmental agencies and other public and private research organizations for collaborative arrangements with pharmaceutical and biotechnology companies, in recruiting and retaining highly qualified scientific, sales and marketing, and management personnel and for licenses to additional technologies. Our competitors, either alone or with their collaborators, may succeed in developing technologies or drugs that are more effective, safer, and more affordable, or more easily administered than ours and may achieve patent protection or commercialize drugs sooner than us. Our competitors may also develop alternative therapies that could further limit the market for any drugs that we may develop. Our failure to compete effectively could have a material adverse effect on our business.

Intellectual Property

We currently hold 47 issued U.S. patents and a significant number of related issued foreign patents. We have also exclusively licensed rights to an additional 28 issued U.S. patents, and a number of related foreign patents. Patents and other proprietary intellectual property rights are an essential element of our business. Our strategy is to file patent applications in the United States and any other country that represents an important potential commercial market to us. In addition, we seek to protect our technology and inventions (and improvements to inventions) that are important to the development of our business. Our patent applications claim proprietary technology, including chemical synthetic or manufacturing methods, drug assays, novel compounds, compositions, formulations and methods of treatment. We also rely upon trade secrets, including technologies that may be used to discover and validate targets, to identify and develop novel drugs, as well as manufacturing or clinical development technologies, among others. We protect our trade secrets by, among other things, requiring employees and third parties who have access to our proprietary information to sign confidentiality and nondisclosure agreements. We are a party to various license agreements that give us rights to use certain technologies in our research and development.

Pimavanserin

To date, 36 U.S. patents have been issued to us that relate to pimavanserin, NUPLAZID and methods of use. Fourteen of these are Orange Book-listed patents that relate to pimavanserin, NUPLAZID and our approved indication, and cover the general formula of the compound, the composition of matter, with claims specifically directed to pimavanserin and salts thereof, the specific polymorph form of pimavanserin, the approved formulations, and the use thereof for treating our approved indication. The composition of matter patent covering pimavanserin and salts thereof currently has an expiration date in 2027, which could be extended to April 2030 with the addition of the patent term extension (PTE) application we have filed and elected to apply to this patent. This PTE application is currently being reviewed by the U.S. Patent and Trademark Office (PTO). The patents covering the polymorph form and the use of pimavanserin or NUPLAZID for our approved indication are currently set to expire between 2022 and 2028. These patent terms include adjustments made by the PTO, but not extensions.

In the United States, under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as “Hatch-Waxman,” we are permitted to extend the term of one U.S. patent for pimavanserin or the use thereof. Patent terms may be subject to change not only due to potential patent term extensions but also to any terminal disclaimer that reduces patent term, as well as other factors. Because the U.S. patent laws and judicial interpretations thereof change, modifications or new interpretations of the laws may impact our patent terms.

The remaining 22 U.S. patents relating to pimavanserin that have been issued to us cover methods of use of pimavanserin for, among other things, treating AD Psychosis, Alzheimer’s disease indications, schizophrenia, bipolar disorder, Lewy body dementia, sleep disorders, hallucinations and delusions, other indications and methods of producing pimavanserin. We also have a significant number of related issued foreign patents that specifically cover pimavanserin and polymorphs thereof in Europe and Asia as well as in Australia, Canada, Mexico and other countries.

We continue to file and prosecute patent applications directed to pimavanserin, formulations of pimavanserin, methods of manufacturing, and to methods of treating various diseases using pimavanserin, either alone or in combination with other agents, worldwide. For example, in late 2019 and in 2020, we obtained and listed in the Orange Book four additional U.S. issued patents, one patent directed to a method of use for our 10 mg tablet, expiring in 2037, and three patents directed to our 34 mg capsule formulation, each expiring in 2038.

We entered into a license agreement in 2006 for certain intellectual property rights from the Ipsen Group that complement the intellectual property portfolio for our serotonin platform, including pimavanserin. We are required to pay to the Ipsen Group royalties of up to 2% of net product sales of NUPLAZID pursuant to the agreement. This obligation terminated in October 2021.

Trofinetide

To date, 10 U.S. patents have been issued and exclusively licensed to us from Neuren Pharmaceuticals that relate to trofinetide and methods of use of trofinetide. Several U.S. patents would be eligible for Orange Book listing, including a composition of matter patent with claims specifically directed to trofinetide or salts thereof and a patent claiming the use of trofinetide for treating Rett syndrome. The composition of matter patent covering trofinetide and salts thereof currently has an expiration date in 2022, and the use patent for treating Rett syndrome has an expiration date in 2032.

Under the license agreement with Neuren, we continue to file and prosecute patent applications directed to trofinetide, formulations of trofinetide, methods of manufacturing and methods of treating Rett syndrome using trofinetide.

Government Regulation

Our business activities, including the manufacturing and marketing of NUPLAZID and our potential products and our ongoing research and development activities, are subject to extensive regulation by numerous governmental authorities in the United States and other countries. Before marketing in the United States, any new drug developed by us must undergo rigorous preclinical testing, clinical trials and an extensive regulatory clearance process implemented by the FDA under the Federal Food, Drug, and Cosmetic Act, as amended. The FDA regulates, among other things, the development, testing, manufacture, safety, efficacy, record keeping, labeling, storage, approval, advertising, promotion, import, export, sale and distribution of biopharmaceutical products. The regulatory review and approval process, which includes preclinical testing and clinical trials of each product candidate, is lengthy, expensive and uncertain. Moreover, government coverage and reimbursement policies will both directly and indirectly impact our ability to successfully commercialize NUPLAZID and any future approved products, and such coverage and reimbursement policies will be impacted by enacted and any applicable future healthcare reform and drug pricing measures. In addition, we are subject to state and federal laws, including, among others, anti-kickback laws, false claims laws, data privacy and security laws, and transparency laws that restrict certain business practices in the pharmaceutical industry.

In the United States, drug product candidates intended for human use undergo laboratory and animal testing until adequate proof of safety is established. Clinical trials for new product candidates are then typically conducted in humans in three sequential phases that may overlap. Phase 1 trials involve the initial introduction of the product candidate into healthy human volunteers. The emphasis of Phase 1 trials is on testing for safety or adverse effects, dosage, tolerance, metabolism, distribution, excretion and clinical pharmacology. Phase 2 involves studies in a limited patient population to determine the initial efficacy of the compound for specific targeted indications, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and safety risks. Once a compound shows initial evidence of effectiveness and is found to have an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to more fully evaluate clinical outcomes. Before commencing clinical investigations in humans, we or our collaborators must submit an Investigational New Drug Application (IND), to the FDA.

Regulatory authorities, Institutional Review Boards and Data Monitoring Committees may require additional data before allowing the clinical studies to commence, continue or proceed from one phase to another, and could demand that the studies be discontinued or suspended at any time if there are significant safety issues. Clinical testing must also meet requirements for clinical trial registration, institutional review board oversight, informed consent, health information privacy, and good clinical practices (GCPs). Additionally, the manufacture of our drug product must be done in accordance with current good manufacturing practices (GMPs).

To establish a new product candidate's safety and efficacy, the FDA requires companies seeking approval to market a drug product to submit extensive preclinical and clinical data, along with other information, for each indication for which the product will be labeled. The data and information are submitted to the FDA in the form of a New Drug Application (NDA), which must be accompanied by payment of a significant user fee unless a waiver or exemption applies. Generating the required data and information for an NDA takes many years and requires the expenditure of substantial resources. Information generated in this process is susceptible to varying interpretations that could delay, limit or prevent regulatory approval at any stage of the process. The failure to demonstrate adequately the quality, safety and efficacy of a product candidate under development would delay or prevent regulatory approval of the product candidate. Under applicable laws and FDA regulations, each NDA submitted for FDA approval is given an internal administrative review within 60 days following submission of the NDA. If deemed sufficiently complete to permit a substantive review, the FDA will "file" the NDA. The FDA can refuse to file any NDA that it deems incomplete or not properly reviewable. The FDA has established internal goals of eight months from submission for priority review of NDAs that cover new product candidates that offer major advances in treatment or provide a treatment where no adequate therapy exists, and 12 months from submission for the standard review of NDAs. However, the FDA is not legally required to complete its review within these periods, these performance goals may change over time and the review is often extended by FDA requests for additional information or clarification. Moreover, the outcome of the review, even if generally favorable, may not be an actual approval but a "complete response letter" that describes additional work that must be done before the NDA can be approved. Before approving an NDA, the FDA can choose to inspect the facilities at which the product is manufactured and will not approve the product unless the manufacturing facility complies with GMPs. The FDA may also audit sites at which clinical trials have been conducted to determine compliance with GCPs and data integrity. The FDA's review of an NDA may also involve

review and recommendations by an independent FDA advisory committee, particularly for novel indications. The FDA is not bound by the recommendation of an advisory committee.

In addition, delays or rejections may be encountered based upon changes in regulatory policy, regulations or statutes governing product approval during the period of product development and regulatory agency review.

Before receiving FDA approval to market a potential product, we or our collaborators must demonstrate through adequate and well-controlled clinical studies that the potential product is safe and effective in the patient population that will be treated. In addition, under the Pediatric Research Equity Act (PREA), an NDA or supplement to an NDA must contain data or a plan to collect such data 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, unless a waiver applies. If regulatory approval of a potential product is granted, this approval will be limited to those disease states and conditions for which the product is approved. Marketing or promoting a drug for an unapproved indication is generally prohibited. Furthermore, FDA approval may entail ongoing requirements for risk management, including post-marketing, or Phase 4, studies. Even if approval is obtained, each marketed product, is subject to payment of a significant annual program user fee and continuing review and periodic inspections by the FDA. Discovery of previously unknown problems with a product, manufacturer or facility may result in restrictions on the product or manufacturer, including labeling changes, warning letters, costly recalls or withdrawal of the product from the market.

Any drug is likely to produce some toxicities or undesirable side effects in animals and in humans when administered at sufficiently high doses and/or for sufficiently long periods of time. Unacceptable toxicities or side effects may occur at any dose level at any time in the course of studies in animals designed to identify unacceptable effects of a product candidate, known as toxicological studies, or during clinical trials of our potential products. The appearance of any unacceptable toxicity or side effect could cause us or regulatory authorities to interrupt, limit, delay or abort the development of any of our product candidates. Further, such unacceptable toxicity or side effects could ultimately prevent a potential product's approval by the FDA or foreign regulatory authorities for any or all targeted indications or limit any labeling claims and market acceptance, even if the product is approved.

In addition, as a condition of approval, the FDA may require an applicant to develop a risk evaluation and mitigation strategy (REMS). A REMS uses risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use (ETASU). ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

We and our collaborators and contract manufacturers also are required to comply with the applicable FDA GMP regulations. GMP regulations include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation. Manufacturing facilities are subject to inspection by the FDA. These facilities must be approved before we can use them in commercial manufacturing of our potential products and must maintain ongoing compliance for commercial product manufacture. The FDA may conclude that we or our collaborators or contract manufacturers are not in compliance with applicable GMP requirements and other FDA regulatory requirements, which may result in delay or failure to approve applications, warning letters, product recalls and/or imposition of fines or penalties.

If a product is approved, we must also comply with post-marketing requirements, including, but not limited to, compliance with advertising and promotion laws enforced by various government agencies, including the FDA's Office of Prescription Drug Promotion, and through such laws as federal and state anti-fraud and abuse laws, including anti-kickback and false claims laws, healthcare information privacy and security laws, post-marketing safety surveillance, and disclosure of payments or other transfers of value to healthcare professionals and entities. In addition, we are subject to other federal and state regulation including, for example, the implementation of corporate compliance programs.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of pharmaceutical products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain.

Outside of the United States, our ability to market a product is contingent upon receiving a marketing authorization from the appropriate regulatory authorities. The requirements governing the conduct of clinical trials, marketing authorization, pricing and reimbursement vary widely from country to country. If the regulatory authority is satisfied that adequate evidence of safety, quality and efficacy has been presented, marketing authorization will be granted. This foreign regulatory approval process involves all of the risks associated with FDA marketing approval discussed above. In addition, foreign regulations may include applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or other transfers of value to healthcare professionals and entities.

Coverage and Reimbursement

Sales of NUPLAZID and of our product candidates, if approved, depend and will depend, in part, on the extent to which such products will be covered by third-party payors, such as government health care programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly limiting coverage and/or reducing reimbursements for medical products and services. A third-party payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage for the drug product. Coverage policies and third-party payor reimbursement rates may change at any time. Therefore, even if favorable coverage and reimbursement status is attained, less favorable coverage policies and reimbursement rates may be implemented in the future. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party payor reimbursement or a decision by a third-party payor to not cover NUPLAZID or any future approved products could reduce physician usage of our products, and have a material adverse effect on our sales, results of operations and financial condition.

In the United States, the Medicare Part D program provides a voluntary outpatient drug benefit to Medicare beneficiaries for certain products. NUPLAZID is available for coverage under Medicare Part D, but the individual Part D plans offer coverage subject to various factors such as those described above. In addition, while Medicare Part D plans have historically included "all or substantially all" drugs in the following designated classes of "clinical concern" on their formularies: anticonvulsants, antidepressants, antineoplastics, antipsychotics, antiretrovirals, and immunosuppressants, the Centers for Medicare & Medicaid Services (CMS), has in the past proposed, but not adopted, changes to this policy. If this policy is changed in the future and if CMS no longer considers the antipsychotic class to be of "clinical concern", Medicare Part D plans would have significantly more discretion to reduce the number of products covered in that class, including coverage of NUPLAZID. Furthermore, private third-party payors often follow Medicare coverage policies and payment limitations in setting their own coverage policies.

Healthcare Laws and Regulations

We are subject to healthcare regulation and enforcement by the federal government and the states and foreign governments in which we conduct our business. The healthcare laws and regulations that may affect our ability to operate include the following:

- The federal Anti-Kickback Statute makes it illegal for any person or entity to knowingly and willfully, directly or indirectly, solicit, receive, offer, or pay any remuneration that is in exchange for or to induce the referral of business, including the purchase, order, lease of any good, facility, item or service for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. The term "remuneration" has been broadly interpreted to include anything of value.

- Federal false claims and false statement laws, including the federal civil False Claims Act, and civil monetary penalties laws, prohibit, among other things, any person or entity from knowingly presenting, or causing to be presented, for payment to, or approval by, federal programs, including Medicare and Medicaid, claims for items or services, including drugs, that are false or fraudulent.
- The U.S. federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), created additional federal criminal statutes that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors or making any false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH), and their implementing regulations, imposes obligations on covered entities, including certain healthcare providers, health plans, and healthcare clearinghouses, and their respective business associates that create, receive, maintain or transmit individually identifiable health information for or on behalf of a covered entity as well as their covered subcontractors, with respect to safeguarding the privacy, security and transmission of individually identifiable health information. In addition, the European Union (EU), has established its own data security and privacy legal framework, including but not limited to the recently adopted European General Data Protection Regulation (EU) 2016/79 (GDPR), which contains new provisions specifically directed at the processing of health information, higher sanctions than previous EU data protection laws and extra-territoriality measures intended to bring non-EU companies under the regulation. We currently conduct clinical trials in the EU and will need to be compliant with these requirements. We anticipate that over time we may expand our business operations to include additional operations in the EU. With such expansion, we would be subject to increased governmental regulation in the EU countries in which we might operate, including the GDPR.
- The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to CMS information related to payments or other transfers of value made to physicians (as defined to include doctors of medicine, dentists, optometrists, podiatrists and chiropractors by such law), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members.

Also, many states have similar laws and regulations, such as anti-kickback and false claims laws that may be broader in scope and may apply regardless of payor, in addition to items and services reimbursed under Medicaid and other state programs. Additionally, we may be subject to state laws that require pharmaceutical companies to comply with the federal government's and/or pharmaceutical industry's voluntary compliance guidelines, state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, state laws that require drug manufacturers to report information on the pricing of certain drugs, state and local laws that require the registration of pharmaceutical sales representatives, as well as state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA.

If we are found to be in violation of any of these laws or any other federal or state regulations, we may be subject to significant administrative, civil and/or criminal penalties, damages, fines, disgorgement, imprisonment, exclusion from federal health care programs, additional reporting requirements and/or oversight, and the curtailment or restructuring of our operations.

Additionally, to the extent that our product is sold in a foreign country, we may be subject to similar foreign laws.

Healthcare Reform

The United States and some foreign jurisdictions are considering or have enacted a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. By way of example, in March 2010, Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act (collectively, the ACA) was signed into law, which intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the ACA of importance to NUPLAZID and our product candidates are:

- 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 government healthcare programs;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively;
- extension of a manufacturer's Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- a Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

There have been executive, judicial and Congressional challenges to certain aspects of the ACA. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the ACA have been enacted. Legislation enacted in 2017, informally titled the Tax Cuts and Jobs Act of 2017 (2017 Tax Act), includes a provision repealing, effective January 1, 2019, 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 that is commonly referred to as the "individual mandate". In addition, the 2020 federal spending package permanently eliminates, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and the medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. The Bipartisan Budget Act of 2018 (the BBA), among other things, amended the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans. On June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the ACA will remain in effect in its current form. Prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how such challenges and the healthcare reform measures of the Biden administration will impact the ACA.

Other legislative changes have been proposed and adopted in the United States since the ACA. Through the process created by the Budget Control Act of 2011, there are automatic reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments, including the Infrastructure Investment and Jobs Act, will remain in effect through 2031 unless additional Congressional action is taken. However, coronavirus disease 2019 (COVID-19) relief support legislation suspended the 2% Medicare sequester from May 1, 2020 through March 31, 2022. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates 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. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to certain providers.

Moreover, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their commercial products. There have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that attempt to implement several of the administration's proposals. The FDA concurrently released a final rule and guidance in September 2020 implementing a portion of the importation executive order providing pathways for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, the U.S. Department of Health and Human Services (HHS) finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of this rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed until January 1, 2023. In addition, on November 20, 2020, CMS issued an interim final rule implementing President Trump's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. As a result of litigation challenging the Most Favored Nation model, on December 27, 2021, CMS published a final rule that rescinded the Most Favored Nation model interim final rule. In July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. However, it is unclear whether these or similar policy initiatives will be implemented in the future. 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.

We expect that healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria and lower reimbursement, and additional downward pressure on the price that we receive for NUPLAZID and any future approved products. Further, it is possible that additional governmental action will be taken in response to the COVID-19 pandemic. We cannot predict what healthcare reform initiatives may be adopted in the future.

Manufacturing and Distribution

We currently outsource, and plan to continue to outsource, manufacturing activities for NUPLAZID, as well as for our existing and future product candidates for development and commercial purposes. We believe this manufacturing strategy will enable us to direct our financial resources to our commercial activities and to the ongoing development of pimavanserin without devoting the substantial resources and capital required to build manufacturing facilities.

In 2015 and 2020, we licensed worldwide intellectual property rights related to pimavanserin in certain indications to Acadia Pharmaceuticals GmbH, our wholly-owned Swiss subsidiary (Acadia GmbH). Our active pharmaceutical ingredient (API), has been manufactured in Switzerland for over 10 years and we anticipate continuing to manufacture in Switzerland. Acadia GmbH manages the worldwide supply chain of pimavanserin API.

Acadia GmbH has contracted with Siegfried AG, to manufacture the API to be used in NUPLAZID for commercial sale. Under the manufacturing agreement, Acadia GmbH has agreed to purchase from Siegfried specified percentages of our commercial requirements of API for the United States and Europe. The parties may also agree in the future on additional services under the manufacturing agreement with respect to non-commercial supply or development activities. The term of the manufacturing agreement ended in December 2021 and renewed for a two-year term and will automatically renew for subsequent two-year terms unless either party provides timely notice of its intent not to renew, or unless the manufacturing agreement is terminated earlier pursuant to its terms. Either party may terminate the manufacturing agreement prior to expiration upon an uncured material breach by the other party, upon the dissolution or liquidation of the other party, the commencement of insolvency procedures that are not dismissed within a certain period of time, the appointment of any receiver, trustee or assignee to take possession of the properties of the other party or the cessation of all or substantially all of the other party's business operations, upon certain continuing patent infringement, regulatory litigation or other legal proceedings involving the manufacture of API, upon a continuing force majeure affecting the other party, or if no services are

currently being provided under the manufacturing agreement. Additionally, if the parties agree on development services under the manufacturing agreement, the parties may terminate such services by mutual agreement if reasonable efforts to achieve the goals of such services fail. Acadia GmbH also may terminate any services under the manufacturing agreement for any reason on 90 days' prior notice to Siegfried, subject to the requirements of the manufacturing agreement.

We have contracted with Patheon Pharmaceuticals Inc. (Patheon), to manufacture NUPLAZID 10 mg tablet and 34 mg capsule drug product for commercial use in the United States. We have also contracted with a second contract manufacturing organization to manufacture NUPLAZID 34 mg drug product for commercial use in the United States. Under the manufacturing agreement with Patheon, we have agreed to purchase from Patheon a specified percentage of our commercial requirements of NUPLAZID for the United States. Under the agreement, Patheon will also perform specified validation services. The term of the manufacturing agreement ends in the first quarter of 2023 and will automatically renew for subsequent two-year terms unless either party provides timely notice of its intent not to renew, or unless the manufacturing agreement is terminated early pursuant to its terms. Each party may terminate the manufacturing agreement prior to expiration upon the uncured material breach by the other party, upon the bankruptcy or insolvency of the other party or in the event of a continuing force majeure event affecting the other party. The manufacturing agreement will also terminate if we provide notice to Patheon that we no longer require manufacturing services because NUPLAZID has been discontinued. Additionally, we may terminate the manufacturing agreement, subject to certain limitations, if any regulatory authority takes any action or raises any objection that prevents us from continuing to commercialize NUPLAZID or takes an enforcement action against Patheon's manufacturing site that relates to NUPLAZID or could reasonably be expected to adversely affect Patheon's ability to supply NUPLAZID, if we determine to discontinue commercialization of NUPLAZID for safety or efficacy reasons, or if Patheon uses any debarred person in performing its service obligations under the manufacturing agreement. We also may terminate the manufacturing agreement for any other reason on three years' prior notice to Patheon. Patheon may terminate the manufacturing agreement if we assign the manufacturing agreement or any of our rights under the manufacturing agreement to a Patheon competitor.

We sell NUPLAZID to a limited number of specialty pharmacies (SPs), and specialty distributors (SDs), which we collectively refer to as our customers. SPs subsequently dispense NUPLAZID to patients based on the fulfillment of a prescription and SDs subsequently sell NUPLAZID to government facilities, long-term care pharmacies, and in-patient hospital pharmacies. Four customers, each based in the United States, accounted for approximately 74% of our total revenue for the year ended December 31, 2021. We have retained third-party service providers to perform a variety of functions related to the distribution of NUPLAZID, including warehousing, customer service, order-taking, invoicing, collections, and shipment and returns processing.

We have contracted with manufacturers to produce clinical supplies of trofinetide to support the development program. If trofinetide or any other product candidate is approved by the FDA or other regulatory agencies for commercial sale, we will need to contract with a third party to manufacture such products for commercial sale in the U.S. and/or in such other jurisdictions.

Sales and Marketing

We have U.S. sales specialists that are focused on promoting NUPLAZID to physicians who treat PDP patients, including neurologists, psychiatrists and healthcare professionals caring for patients in long-term care setting. This sales force is supported by an experienced sales leadership team. Our experienced commercial team comprised of experienced professionals in marketing, key account management, patient access services, commercial operations, and sales force planning and management. In addition, our commercial infrastructure includes capabilities in manufacturing, health outcomes, medical affairs, quality control, and compliance.

We launched NUPLAZID in May 2016, and our focus is to continue to establish NUPLAZID as the standard of care for patients with PDP. In order to help us achieve this goal, we are continuing to increase awareness of NUPLAZID's benefits in PDP with a prescriber and patient education campaign consisting of key opinion leader speaker programs, attendance at medical meetings, digital outreach, multimedia campaigns, and direct-to-patient programs.

In selected markets outside of the United States in which NUPLAZID may be approved, if any, we may choose to commercialize NUPLAZID independently or by establishing one or more strategic alliances.

Long-Lived Assets

Our tangible long-lived assets are comprised of intangible assets and property and equipment. Our property and equipment totaled $8.0 million, $9.2 million, and $3.2 million as of December 31, 2021, 2020 and 2019, respectively. All of our tangible long-lived assets are located in the United States. Our intangible assets, comprised of right-of-use assets and other intangibles acquired, totaled $58.3 million, $48.4 million and $12.1 million as of December 31, 2021, 2020 and 2019, respectively.

Employees and Human Capital

Employees. At December 31, 2021, we had a total of 514 employees, 512 of whom were full-time. We employ physicians, scientists and professionals in research and development, clinical, regulatory, manufacturing, marketing, sales, finance, legal and other functions that are important to our business. We also will continue to use temporary workers in certain instances in order to maximize our employment flexibility in light of our business needs. Additionally, when we think it is in the best interest of our business we will rely upon external advisers and consultants rather than our employees.

Employee Engagement, Benefits & Development. We believe that our future success is dependent upon our ability to recruit, hire and retain exceptional employees. We provide our employees with competitive cash compensation, opportunities to own equity, and an employee benefit program that promotes well-being, including healthcare, retirement planning and paid vacation time. We also provide employees with opportunities to continue their education and growth, including leadership development and tuition reimbursement. In order to receive feedback from our employees and evaluate our level of employee engagement, we regularly conduct an employee survey.

Diversity & Inclusion. We value diversity across our workforce and we will continue to focus on diversity and inclusion initiatives. We seek to have an inclusive and positive culture that is centered on our shared corporate mission and values.

Item 1A. *Risk Factors.*

You should consider carefully the following information about the risks described below, together with the other information contained in this Annual Report and in our other public filings, in evaluating our business. If any of the following risks actually occurs, our business, financial condition, results of operations, and future growth prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock would likely decline.

Summary Risk Factors

We face risks and uncertainties related to our business, many of which are beyond our control. In particular, risks associated with our business include:

- Our prospects are highly dependent on the successful commercialization of NUPLAZID. To the extent NUPLAZID is not commercially successful, our business, financial condition and results of operations may be materially adversely affected and the price of our common stock may decline.
- If we do not obtain regulatory approval of pimavanserin for other indications in addition to treatment of PDP in the U.S., or for any indication in foreign jurisdictions, or regulatory approval of trofinetide for Rett syndrome, we will not be able to market pimavanserin for other indications in the U.S. or in other jurisdictions or market trofinetide at all, which will limit our commercial revenues.
- Even though the FDA has granted approval of NUPLAZID for the treatment of hallucinations and delusions associated with PDP, the terms of the approval may limit its commercial potential. Additionally, NUPLAZID is still subject to substantial, ongoing regulatory requirements.
- We currently market and sell NUPLAZID, our only commercial product, and rely on a limited network of third-party distributors and pharmacies. If we are unable to continue to effectively commercialize NUPLAZID, we may not be able to generate adequate product revenues.
- If we are unable to effectively train and equip our sales force, our ability to successfully commercialize NUPLAZID will be harmed.
- NUPLAZID may not gain maximal acceptance among physicians, patients, and the medical community, thereby limiting our potential to generate revenues.

- Our ability to generate product revenues will be diminished if NUPLAZID does not receive coverage from payors or sells for inadequate prices, or if patients have unacceptably high co-pay amounts.
- Delays, suspensions and terminations in our clinical trials could result in increased costs to us and delay our ability to generate product revenues.
- Healthcare reform measures may negatively impact our ability to sell NUPLAZID or our product candidates, if approved, profitably.
- If we are unable to attract, retain, and motivate key management, research and development, and sales and marketing personnel, our drug development programs, our research and discovery efforts, and our commercialization plans may be delayed and we may be unable to successfully commercialize our products, including NUPLAZID, or develop our product candidates, including pimavanserin for indications beyond PDP.
- We expect our net losses to continue for the next few years and are unable to predict the extent of future losses or when we will become profitable, if ever.
- If we fail to obtain the capital necessary to fund our operations, we will be unable to successfully continue the development and commercialization of NUPLAZID or successfully develop and commercialize our other product candidate opportunities.
- We expect that our results of operations will fluctuate, which may make it difficult to predict our future performance from period to period.
- Public health threats, including the continuing COVID-19 pandemic, have impacted our clinical trials and could have an adverse effect on our operations and financial results, or may cause us to modify or suspend our financial guidance.
- We previously have depended, and in the future may depend, on collaborations with third parties to develop and commercialize selected product candidates other than pimavanserin, and we have limited control over how those third parties conduct development and commercialization activities for such product candidates.
- We currently depend, and in the future will continue to depend, on third parties to manufacture NUPLAZID, trofinetide and our other product candidates. If these manufacturers fail to provide us or our collaborators with adequate supplies of clinical trial materials and commercial product or fail to comply with the requirements of regulatory authorities, we may be unable to develop or commercialize NUPLAZID, trofinetide or any other product candidates.
- If we fail to comply with the obligations in agreements under which we license intellectual property rights from third parties, we could lose the right to develop certain of our product candidates.
- Our ability to compete may decline if we do not adequately protect our proprietary rights.
- If our competitors develop and market products that are more effective than NUPLAZID or our product candidates, they may reduce or eliminate our commercial opportunity.
- Our stock price historically has been, and is likely to remain, highly volatile.

Risks Related to Our Business

Our prospects are highly dependent on the successful commercialization of NUPLAZID. To the extent NUPLAZID is not commercially successful, our business, financial condition and results of operations may be materially adversely affected and the price of our common stock may decline.

NUPLAZID is our only drug that has been approved for sale and it has only been approved for the treatment of hallucinations and delusions associated with PDP, in the U.S. since April 2016. We are currently focusing most of our activities and resources on NUPLAZID, because we believe that our prospects are highly dependent on, and the vast majority of the value of our company relates to, our ability to successfully commercialize NUPLAZID in the U.S.

Successful commercialization of NUPLAZID is subject to many risks, and there is no guarantee that we will be able to successfully commercialize NUPLAZID for additional approved indications beyond PDP. There are numerous examples of failures to meet high expectations of market potential, including by pharmaceutical companies with more experience and resources than us. While we have established our commercial team and have hired our U.S. sales force, we will need to further expand and develop the team in order to successfully commercialize NUPLAZID for additional indications. Even if

we are successful in developing our commercial team, there are many factors that could cause the commercialization of NUPLAZID to be unsuccessful, including a number of factors that are outside our control. Because no drug has previously been approved by the FDA for the treatment of hallucinations and delusions associated with PDP, it is especially difficult to estimate NUPLAZID's market potential for its approved indication and potential additional indications. The commercial success of NUPLAZID currently depends on the extent to which patients and physicians recognize and diagnose PDP and accept and adopt NUPLAZID as a treatment for hallucinations and delusions associated with PDP, and we do not know whether our or others' estimates in this regard will be accurate. For example, if the patient population suffering from hallucinations and delusions associated with PDP is smaller than we estimate or if physicians are unwilling to prescribe or patients are unwilling to take NUPLAZID, perceived safety issues, or for other reasons, the commercial potential of NUPLAZID will be limited. We have limited information about how physicians, patients and payors have responded and will respond to the pricing of NUPLAZID. We have changed, and may continue to change, the price of NUPLAZID from time to time. Physicians may not prescribe NUPLAZID and patients may be unwilling to use NUPLAZID if coverage is not provided or reimbursement is inadequate to cover a significant portion of the cost. Additionally, any negative publicity related to NUPLAZID, or negative development for NUPLAZID in our post-marketing commitments, in clinical development in additional indications, or in regulatory processes in other jurisdictions, may adversely impact the commercial results and potential of NUPLAZID. Thus, significant uncertainty remains regarding the commercial potential of NUPLAZID.

In addition, our business could be adversely affected by the effects of public health threats, including the COVID-19 pandemic. During 2021, sales of NUPLAZID were negatively impacted by ongoing conditions related to the pandemic, including a reduction in patient office visits and a continuing reduced occupancy rates at long-term care facilities. While we observed incremental improvements in some of these factors during the latter part of the year, their levels are still meaningfully below where they were pre-pandemic. It remains difficult to predict the duration of the pandemic's impact and the pace of recovery, and no assurances can be given that the pandemic will not continue to have additional negative impacts on our business, results of operations, financial condition and prospects. If the commercialization of NUPLAZID is less successful than expected or perceived as disappointing, our stock price could decline significantly and the long-term success of the product and our company could be harmed.

If we do not obtain regulatory approval of pimavanserin for other indications in addition to treatment of PDP in the U.S., or for any indication in foreign jurisdictions, or regulatory approval of trofinetide for Rett syndrome, we will not be able to market pimavanserin for other indications in the U.S. or in other jurisdictions or market trofinetide at all, which will limit our commercial revenues.

While pimavanserin has been approved in the U.S. by the FDA for the treatment of hallucinations and delusions associated with PDP, it has not been approved by the FDA for any other indications, and it has not been approved in any other jurisdiction for this indication or for any other indication. In order to market pimavanserin for other indications or in other jurisdictions, we must obtain regulatory approval for each of those indications and in each of the applicable jurisdictions, and we may never be able to obtain such approval. Approval of NUPLAZID by the FDA for the treatment of hallucinations and delusions associated with PDP does not ensure that foreign jurisdictions will also approve NUPLAZID for that indication, nor does it ensure that NUPLAZID will be approved by the FDA for any other indication. For example, following the successful completion of our Phase 3 HARMONY study, we submitted an sNDA to the FDA for the treatment of DRP on June 3, 2020. In July 2020 the FDA notified us of its filing of our sNDA with a filing date of August 2, 2020 and a PDUFA target action date of April 3, 2021. As part of its filing communication, the FDA advised us that it had not identified any potential review issues at that point in its evaluation and at that time was not planning to hold an Advisory Committee meeting. On March 3, 2021, we received a notification from the FDA stating that it had identified deficiencies that preclude discussion of labeling and post-marketing requirements/commitments. The notification did not specify the deficiencies identified by the FDA. On April 2, 2021, we received a CRL from the FDA, indicating that the FDA had completed its review of the application and determined that it could not be approved in its present form. In the CRL, the FDA cited a lack of statistical significance in some of the subgroups of dementia in the HARMONY study, as well as insufficient numbers of patients with certain less common dementia subgroups as lack of substantial evidence of effectiveness to support approval. The FDA also stated in the CRL that it considers Alzheimer's disease psychosis study -019 to not be adequate and well controlled, citing that it was a single center study with no type I error control of secondary endpoints in which certain protocol deviations occurred. We conducted an end of review (Type A) meeting at which the FDA reiterated, as stated in the CRL, that pimavanserin should be studied by individual subgroups of DRP, and advised us that the best path forward is to conduct an additional clinical study in each of the subgroups for which we seek approval. However, the FDA was also open to reviewing additional analyses from the HARMONY and -019 studies in support of a potential resubmission for individual subgroups without additional clinical studies. We subsequently held additional meetings (Type B) with the FDA and further discussed the potential for a resubmission based on additional analyses supporting a potential indication for treatment of ADP

specifically. In February 2022, we made a resubmission to the FDA for NUPLAZID for the treatment of hallucinations and delusions associated with ADP and to make a complete response to the issues raised in the FDA's CRL.

We initiated a Phase 3 program for pimavanserin as an adjunctive treatment for MDD in April 2019. In July 2020, we announced that our Phase 3 CLARITY study, which combined two identical, double-blind, placebo-controlled studies, did not achieve statistical significance on the primary endpoint. As a result, at this time we do not plan on initiating any additional Phase 3 studies to evaluate pimavanserin for adjunctive use with SSRI/SNRI drugs for the treatment of MDD.

We initiated the Phase 3 ADVANCE-2 study of pimavanserin for the treatment of the negative symptoms of schizophrenia in August 2020. There is no guarantee that our ongoing study will be successful, or that the FDA or any regulatory authority in foreign jurisdictions will approve pimavanserin for that indication.

In December 2021, we announced positive results from our pivotal Phase 3 LAVENDER study. The study demonstrated a statistically significant improvement over placebo for both co-primary endpoints as well as key secondary endpoint. We plan to submit to the FDA an NDA for trofinetide for the treatment of Rett syndrome around mid-year 2022, but there is no guarantee that FDA will approve trofinetide for the treatment of Rett syndrome.

The research, testing, manufacturing, labeling, approval, sale, import, export, marketing, and distribution of pharmaceutical product candidates are subject to extensive regulation by the FDA and other regulatory authorities in the U.S. and other countries, whose regulations differ from country to country. We will be required to comply with different regulations and policies of the jurisdictions where we seek approval for our product candidates, and we have not yet identified all of the requirements that we will need to satisfy to submit NUPLAZID for approval for other indications or in other jurisdictions or to submit trofinetide for approval for Rett syndrome. This will require additional time, expertise and expense, including the potential need to conduct additional studies or development work for other jurisdictions beyond the work that we have conducted to support our NDA submission in PDP. In addition, strategic considerations need to be taken into account when determining whether and when to submit NUPLAZID for approval in other jurisdictions. For example, in the fourth quarter of 2016, the European Medicines Agency (EMA), approved our proposed pediatric investigation plan related to our planned submission of a marketing authorization application (MAA), for NUPLAZID for the treatment of PDP in Europe. However, in light of our continuing clinical development of pimavanserin in indications other than in PDP, and the time-limited data exclusivity currently granted by the EMA that commences on first approval of a product in Europe, we deferred submission of the MAA and we do not yet have a revised estimate of when we will make that filing. If we do not receive marketing approval for NUPLAZID for any other indication or from any regulatory agency outside of the U.S. or any marketing approval for trofinetide, we will never be able to commercialize NUPLAZID for any other indication in the U.S. or for any indication in any other jurisdiction or be able to commercialize trofinetide at all. Even if we do receive additional regulatory approvals, we may not be successful in commercializing those opportunities.

If the results or timing of regulatory filings, the regulatory process, regulatory developments, clinical trials or preclinical studies, or other activities, actions or decisions related to NUPLAZID do not meet our or others' expectations, the market price of our common stock could decline significantly.

Even though the FDA has granted approval of NUPLAZID for the treatment of hallucinations and delusions associated with PDP, the terms of the approval may limit its commercial potential. Additionally, NUPLAZID is still subject to substantial, ongoing regulatory requirements.

Even though the FDA has granted approval of NUPLAZID, the scope and terms of the approval may limit our ability to commercialize NUPLAZID and, therefore, our ability to generate substantial sales revenues. The FDA has approved NUPLAZID only for the treatment of hallucinations and delusions associated with PDP. The label for NUPLAZID also contains a "boxed" warning that elderly patients with DRP treated with antipsychotic drugs are at an increased risk of death, and that NUPLAZID is not approved for the treatment of patients with DRP unrelated to the hallucinations and delusions associated with PDP. This "boxed" warning may discourage physicians from prescribing NUPLAZID to patients diagnosed with PDP, including those with dementia.

In connection with the FDA approval, we committed to conduct the following post-marketing studies: (i) a randomized, placebo-controlled withdrawal study in patients treated with NUPLAZID, (ii) studies to collect additional data to add to the NUPLAZID safety database from an aggregate of at least 500 predominantly frail and elderly subjects on NUPLAZID in one or more randomized, placebo-controlled studies of eight or more weeks duration, (iii) a drug-drug interaction study with NUPLAZID and a strong CYP3A4 inducer, and (iv) re-analysis of tissue samples from certain previously conducted preclinical studies. We have completed the (i) a randomized, placebo-controlled withdrawal study in patients treated with NUPLAZID, (iii) drug-drug interaction study with NUPLAZID and a strong CYP3A4 inducer and (iv) the re-analysis of tissue samples. We have received FDA approval of an sNDA for labeling revisions related to the completed CYP3A4 study. If we fail to comply with our remaining post-marketing commitment, or if the results of the post-marketing studies, or any other ongoing or planned clinical studies of NUPLAZID, are negative, the FDA could decide to withdraw approval, add warnings or narrow the approved indication in the product label.

The manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for NUPLAZID will also continue to be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with current good manufacturing processes, good clinical practices, international council for harmonization guidelines and good laboratory practices, which are regulations and guidelines enforced by the FDA for all of our nonclinical and clinical development and for any clinical trials that we conduct post-approval.

Discovery of any issues post-approval, including any safety concerns, such as unexpected side effects or drug-drug interaction problems, adverse events of unanticipated severity or frequency, or concerns over misuse or abuse of the product, problems with the facilities where the product is manufactured, packaged or distributed, or failure to comply with regulatory requirements, may result in, among other things, restrictions on NUPLAZID or on us, including:

- withdrawal of approval, addition of warnings or narrowing of the approved indication in the product label;
- requirement of a Risk Evaluation and Mitigation Strategy to mitigate the risk of off-label use in populations where the FDA may believe that the potential risks of use may outweigh its benefits;
- voluntary or mandatory recalls;
- warning letters;
- suspension of any ongoing clinical studies;
- refusal by the FDA or other regulatory authorities to approve pending applications or supplements to approved applications filed by us, or suspension or revocation of product approvals;
- restrictions on operations, including restrictions on the marketing or manufacturing of the product or the imposition of costly new manufacturing requirements; or
- seizure or detention, or refusal to permit the import or export of products.

If any of these actions were to occur, we may have to discontinue the commercialization of NUPLAZID, limit our sales and marketing efforts, conduct further post-approval studies, and/or discontinue or change any other ongoing or planned clinical studies, which in turn could result in significant expense and delay or limit our ability to generate sales revenues.

NUPLAZID has only been studied in a limited number of patients and in limited populations. As we continue to commercialize NUPLAZID, it is becoming available to a much larger number of patients and in broader populations, and we do not know whether the results of NUPLAZID use in such larger number of patients and broader populations will be consistent with the results from our clinical studies.

Prior to commencing our commercial launch of NUPLAZID in May 2016, NUPLAZID was administered only to a limited number of patients and in limited populations in clinical studies, including our successful pivotal -020 Phase 3 trial with NUPLAZID for the treatment of PDP. We do not know whether the results, when broader populations are exposed to NUPLAZID, including results related to safety and efficacy, will be consistent with the results from the clinical studies of NUPLAZID that served as the basis for its approval. New data relating to NUPLAZID, including from adverse event reports and post-marketing studies in the U.S., and from other ongoing clinical studies, may result in changes to the product label and may adversely affect sales, or result in withdrawal of NUPLAZID from the market. The FDA and regulatory authorities in other jurisdictions may also consider the new data in reviewing NUPLAZID marketing applications for indications other than

in PDP and/or in other jurisdictions, or impose additional post-approval requirements. If any of these actions were to occur, it could result in significant expense and delay or limit our ability to generate sales revenues.

We currently market and sell NUPLAZID, our only commercial product, and rely on a limited network of third-party distributors and pharmacies. If we are unable to continue to effectively commercialize NUPLAZID, we may not be able to generate adequate product revenues.

NUPLAZID is our only drug that has been approved for sale by any regulatory body, and it became available for prescription in the U.S. in May 2016. In order to successfully market NUPLAZID, we must continue to develop our sales, marketing, managerial, compliance, and related capabilities or make arrangements with third parties to perform these services. If we are unable to maintain and develop adequate sales, marketing, and distribution capabilities, whether independently or with third parties, we may not be able to appropriately commercialize NUPLAZID and may not become profitable.

We employ our own internal specialty sales force to commercialize NUPLAZID for the treatment of PDP as part of our commercialization strategy in the U.S. We will need to refine and further develop our sales force as we continue our commercialization efforts, and we will be competing with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and sales personnel. These efforts will continue to be expensive and time-consuming, and we cannot be certain that we will be able to successfully refine and further develop our sales force. If we receive marketing approval for pimavanserin in ADP, we will need to increase our U.S. sales force significantly, and expand our commercial, medical affairs and general and administrative support functions to support commercialization for that indication.

Additionally, our strategy in the U.S. includes distributing NUPLAZID solely through a limited network of third-party specialty distributors and specialty pharmacies. While we have entered into agreements with each of these distributors and pharmacies to distribute NUPLAZID in the U.S., they may not perform as agreed or they may terminate their agreements with us. Also, we may need to enter into agreements with additional distributors or pharmacies, and there is no guarantee that we will be able to do so on commercially reasonable terms or at all. If we are unable to maintain and, if needed, expand, our network of specialty distributors and specialty pharmacies, we would be exposed to substantial distribution risk.

In the event we are unable to maintain, or expand, if needed, our commercial team, including our U.S. sales force, or maintain and, if needed, expand, our network of specialty distributors and specialty pharmacies, our ability to effectively commercialize NUPLAZID and generate product revenues would be limited.

If we are unable to effectively train and equip our sales force, our ability to successfully commercialize NUPLAZID will be harmed.

NUPLAZID is the first drug approved by the FDA for the treatment of hallucinations and delusions associated with PDP. As a result, we are and will continue to be required to expend significant time and resources to train our sales force to be credible, persuasive, and compliant with applicable laws in marketing NUPLAZID for the treatment of hallucinations and delusions associated with PDP to neurologists, psychiatrists, and pharmacists and physicians in long-term care facilities. In addition, we must ensure that consistent and appropriate messages about NUPLAZID are being delivered to our potential customers by our sales force. If we are unable to effectively train our sales force and equip them with effective materials, including medical and sales literature to help them inform and educate potential customers about the benefits of NUPLAZID and its proper administration, our efforts to successfully commercialize NUPLAZID could be put in jeopardy, which would negatively impact our ability to generate product revenues.

NUPLAZID may not gain maximal acceptance among physicians, patients, and the medical community, thereby limiting our potential to generate revenues.

The degree of market acceptance by physicians, healthcare professionals and third-party payors of NUPLAZID, and any other product for which we obtain regulatory approval, and our profitability and growth, will depend on a number of factors, including:

- the ability to provide acceptable evidence of safety and efficacy;
- the scope of the approved indication(s) for the product;
- the inclusion of any warnings or contraindications in the product label;
- the relative convenience and ease of administration;

- the prevalence and severity of any adverse side effects;
- the availability of alternative treatments;
- pricing and cost effectiveness, which may be subject to regulatory control;
- effectiveness of our or our collaborators' sales and marketing strategy; and
- our ability to obtain sufficient third-party insurance coverage or adequate reimbursement levels.

If a product does not provide a treatment regimen that is at least as beneficial as the current standard of care or otherwise does not provide patient benefit, that product will not achieve market acceptance and will not generate sufficient revenues to achieve or maintain profitability.

With respect to NUPLAZID specifically, successful commercialization will depend on whether and to what extent physicians, long-term care facilities and pharmacies, over whom we have no control, determine to utilize NUPLAZID. NUPLAZID is available to treat hallucinations and delusions associated with PDP, an indication for which no other FDA-approved pharmaceutical treatment currently exists. Because of this, it is particularly difficult to estimate NUPLAZID's market potential and how physicians, payors and patients will respond to changes in the price of NUPLAZID. Additionally, NUPLAZID net sales for the year ended December 31, 2021 were negatively impacted due to the COVID-19 pandemic, and the continuing effects of COVID-19 on NUPLAZID net sales are difficult to assess or predict at this time. Industry sources and analysts have a divergence of estimates for the near- and long-term market potential of NUPLAZID, and a variety of assumptions directly impact the estimates for NUPLAZID's market potential, including assumptions regarding the prevalence of PDP, the rate of diagnosis of PDP, the prevalence and rate of hallucinations and delusions in patients diagnosed with PDP, the rate of physician adoption of NUPLAZID, the potential impact of payor restrictions regarding NUPLAZID, and patient adherence and compliance rates. Small differences in these assumptions can lead to widely divergent estimates of the market potential of NUPLAZID. For example, certain research suggests that patients with Parkinson's disease may be hesitant to report symptoms of PDP to their treating physicians for a variety of reasons, including apprehension about societal stigmas relating to mental illness. Research also suggests that physicians who typically treat patients with Parkinson's disease may not ask about or identify symptoms of PDP. For these reasons, even if PDP occurs in high rates among patients with Parkinson's disease, it may be underdiagnosed. Even if PDP is diagnosed, physicians may not prescribe treatment for hallucinations and delusions associated with PDP, and if they do prescribe treatment, they may prescribe other drugs, even though they are not approved in PDP, instead of NUPLAZID. In addition, even if NUPLAZID is prescribed for the treatment of hallucinations and delusions associated with PDP, issues may arise with respect to patient adherence and compliance rates. If patients do not adhere to the recommended dosing of NUPLAZID, patients and physicians may believe that NUPLAZID is less effective, and as a result they may stop taking it and prescribing it.

The label for NUPLAZID also contains a "boxed" warning that elderly patients with DRP treated with antipsychotic drugs are at an increased risk of death, and that NUPLAZID is not approved for the treatment of patients with DRP unrelated to the hallucinations and delusions associated with PDP. There has also been recent attention to publicly reported deaths of patients that were prescribed NUPLAZID, and the FDA conducted an evaluation of available information about NUPLAZID. On September 20, 2018 the U.S. FDA issued a statement concluding: "The U.S. FDA has completed a review of all post marketing reports of deaths and serious adverse events (SAEs) reported with the use of NUPLAZID. Based on an analysis of all available data, FDA did not identify any new or unexpected safety findings with NUPLAZID, or findings that are inconsistent with the established safety profile currently described in the drug label. After a thorough review, FDA's conclusion remains unchanged that the drug's benefits outweigh its risks for patients with hallucinations and delusions of Parkinson's disease psychosis." Although the FDA did not identify any new or unexpected safety risks, the FDA indicated that some potentially concerning prescribing patterns were observed, such as the concomitant use of other antipsychotic drugs or drugs that can cause QT prolongation, a potential cause of heart rhythm disorder. The FDA reminded health care providers to be aware of the risks described in the NUPLAZID prescribing information and that none of the other antipsychotic medications are approved for the treatment of PD psychosis. Regardless, perceptions that NUPLAZID is unsafe, even if unfounded, may discourage physicians from prescribing or patients from taking NUPLAZID.

The commercial success of NUPLAZID depends on acceptance by patients and physicians, and there are a number of factors that could skew our or others' estimates about prescribing behaviors and market adoption.

Our ability to generate product revenues will be diminished if NUPLAZID does not receive coverage from payors or sells for inadequate prices, or if patients have unacceptably high co-pay amounts.

Patients who are prescribed medicine for the treatment of their conditions generally rely on third-party payors, including governmental healthcare programs, such as Medicare and Medicaid, managed care organizations and commercial payors, among others, to reimburse all or part of the costs associated with their prescription drugs. Coverage and adequate reimbursement from third-party commercial payors is critical to product acceptance. Coverage decisions may depend upon clinical and economic standards that disfavor drug products when lower cost therapeutic alternatives are already available or subsequently become available. Even with coverage for NUPLAZID, or other products we may market, the resulting reimbursement payment rates might not be adequate or may require co-payments that patients find unacceptably high. Patients may not use NUPLAZID if coverage is not provided or reimbursement is inadequate to cover a significant portion of its cost.

In addition, the market for NUPLAZID depends significantly on access to third-party payors' drug formularies, or lists of medications for which third-party payors provide coverage and reimbursement. The industry competition to be included in such formularies often leads to downward pricing pressures on pharmaceutical companies. Also, third-party payors may refuse to include a particular branded drug in their formularies or otherwise restrict patient access to a branded drug when a less costly alternative is available, even if not approved for the indication for which NUPLAZID is approved.

In many foreign countries, particularly the countries of the European Union, the pricing of prescription drugs is subject to government control. In some non-U.S. jurisdictions, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. We may face competition from lower-priced products in foreign countries that have placed price controls on pharmaceutical products. In addition, there may be importation of foreign products that compete with NUPLAZID, and any other products we may market, which could negatively impact our profitability.

Third-party payors, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. The current environment is putting pressure on companies to price products below what they may feel is appropriate. Selling NUPLAZID at less than an optimized price could impact our revenues and overall success as a company. We have changed, and may continue to change, the price of NUPLAZID from time to time, however, we do not know if the price we have selected, or may select in the future, for NUPLAZID is or will be the optimized price. Additionally, we do not know whether and to what extent third-party payors will react to any possible future changes in the price of NUPLAZID. In the U.S., no uniform policy of coverage and reimbursement for drug products exists among third-party payors. Further, one payor's determination to provide coverage and reimbursement for a product does not assure that other payors also will provide coverage and reimbursement for the product. Therefore, coverage and reimbursement for NUPLAZID may differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of NUPLAZID to each payor separately, with no assurance that coverage will be obtained. Coverage policies and third-party payor reimbursement rates may change at any time. Therefore, even if favorable coverage and reimbursement status is attained, less favorable coverage policies and reimbursement rates may be implemented in the future. If we are unable to obtain coverage of, and adequate payment levels for, NUPLAZID or any other products we may market to third-party payors, physicians may limit how much or under what circumstances they will prescribe or administer them and patients may decline to purchase them. This in turn could affect our ability to successfully commercialize NUPLAZID, or any other products we may market, and thereby adversely impact our profitability, results of operations, financial condition, and future success.

There is no guarantee that future studies with pimavanserin will be successful.

The historical rate of failures for product candidates in clinical development is extremely high. In November 2012, we announced successful results from the Phase 3 -020 Study of pimavanserin for PDP. Additionally, in December 2016, we announced positive top-line results from our Phase 2 exploratory study of pimavanserin in patients with AD Psychosis, those results may not be predictive of the results of any additional studies that we are currently undertaking or may undertake in the future with pimavanserin, including the post-marketing studies we committed to conduct in connection with FDA approval of NUPLAZID and the ongoing studies of pimavanserin in various indications. We believe that pimavanserin also may have utility in indications other than in PDP, such as in ADP and schizophrenia. However, prior to the Phase 3 HARMONY study that we initiated in the fourth quarter of 2017, which was stopped early for efficacy in September 2019, we had never tested pimavanserin in clinical studies where the primary outcome was for the indication of DRP, and prior to the studies in schizophrenia that we initiated in the fourth quarter of 2016, we had only conducted a Phase 2 trial for pimavanserin as a co-therapy treatment in schizophrenia. There is no guarantee that we will have the same level of success with pimavanserin in other studies that we had with the -020 Study, the HARMONY study and the ADVANCE study. For example, in July 2020 we announced top-line results from the Phase 3 CLARITY study evaluating pimavanserin as an adjunctive treatment with SSRI/SNRI drugs in MDD. In this study pimavanserin did not achieve statistical significance on the primary endpoint. Further, there is no guarantee that we will be successful at all in ongoing or future studies for additional indications or in our post-marketing studies, or that future results of studies of NUPLAZID for treatment in PDP or for other indications will be positive. Moreover, there can be no assurance that a positive study outcome will ultimately result in approval by the FDA.

If we do not successfully complete additional development of NUPLAZID, we will be unable to market and sell NUPLAZID or products derived from it for indications other than the treatment of hallucinations and delusions associated with PDP, or to generate related product revenues.

We are solely responsible for the development and commercialization of pimavanserin.

We have full responsibility for the pimavanserin program throughout the world. We expect our research and development costs for continued development of pimavanserin to be substantial. We are currently undertaking ongoing development work for pimavanserin, including clinical trials of pimavanserin for indications other than in PDP. In the event of approval for additional indications, we would need to add significant resources, and possibly raise additional capital, in order to further commercialize pimavanserin, and to conduct the necessary sales and marketing activities, and to conduct further development activities. Our current strategy is to continue to commercialize NUPLAZID for the treatment of hallucinations and delusions associated with PDP in the U.S. using our specialty sales force focused primarily on neurologists, a small group of psychiatrists, and pharmacists and physicians in long-term care facilities who treat PDP patients. If we receive marketing approval for pimavanserin in ADP, we will need to increase our U.S. sales force significantly, and expand our commercial, medical affairs and general and administrative support functions in connection with commercializing pimavanserin in ADP. In addition, if we are approved to commercialize NUPLAZID in markets outside of the U.S., we may need to establish one or more strategic alliances in the future for that purpose. Without future additional resources or collaboration partners in the U.S. and abroad, we might not be able to realize the full value of NUPLAZID.

Furthermore, even though NUPLAZID is approved for the treatment of hallucinations and delusions associated with PDP, a failure in a subsequent pimavanserin study for another indication, including our ongoing studies in schizophrenia and our previous studies in depression, or any additional studies that may be required in ADP, or a failure in our post-marketing studies could harm our ability to successfully market NUPLAZID for the treatment of hallucinations and delusions associated with PDP or could lead to it being withdrawn from the market. If we are unable to develop pimavanserin for other indications, we may not be able to maximize the potential of the compound and that could have a material adverse effect on our future revenues and our success as a company.

Pimavanserin is currently in late-stage development for additional indications other than in PDP, and we have completed Phase 3 development of trofinetide for Rett syndrome. Drug development is a long, expensive and unpredictable process with a high risk of failure.

Preclinical testing and clinical trials are long, expensive and unpredictable processes that can be subject to delays. It may take several years to complete the preclinical testing and clinical development necessary to commercialize a drug, and delays or failure can occur at any stage. Preliminary, initial, top-line or interim results of clinical trials do not necessarily predict final results and such results may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final results. In addition, success in preclinical testing and

early clinical trials does not ensure that later clinical trials will be successful. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in advanced clinical trials even after promising results in earlier trials.

Our drug development programs are at various stages of development and the historical rate of failures for product candidates is extremely high. In fact, we had an unsuccessful Phase 3 trial with NUPLAZID in 2009. An unfavorable outcome in any of our ongoing or future development efforts or in the post-marketing studies for NUPLAZID could be a major set-back for the program and for us, generally. In particular, an unfavorable outcome in our NUPLAZID program or in the post-marketing studies may require us to delay, devote additional substantial resources to, reduce the scope of, or eliminate this program and could have a material adverse effect on us and the value of our common stock.

In addition, based on positive top-line results from CLARITY, a Phase 2 study evaluating pimavanserin as an adjunctive treatment for MDD, we initiated our Phase 3 CLARITY program, consisting of two Phase 3 studies, CLARITY-2 and CLARITY-3, evaluating pimavanserin as an adjunctive treatment with SSRI/SNRI drugs for MDD. Despite the positive results observed in the Phase 2 CLARITY study, our Phase 3 CLARITY study, did not achieve statistical significance on the primary endpoint. In July 2019, we announced top-line results from the Phase 3 ENHANCE study evaluating pimavanserin as a treatment in inadequate response schizophrenia. In this study pimavanserin did not achieve statistical significance on either the primary endpoint or the key secondary endpoint.

Following the successful completion of our Phase 3 HARMONY study, we submitted an sNDA to the FDA for the treatment of DRP on June 3, 2020. In July 2020 the FDA advised us that it had not identified any potential review issues at that point in its evaluation. On April 2, 2021, we received a CRL indicating that the FDA had completed its review of the application and determined that it could not be approved in its present form. In the CRL, the FDA cited a lack of statistical significance in some of the subgroups of dementia in the HARMONY study, as well as insufficient numbers of patients with certain less common dementia subgroups as lack of substantial evidence of effectiveness to support approval. The FDA also stated in the CRL that it considers Alzheimer's disease psychosis study -019 to not be adequate and well controlled, citing that it was a single center study with no type I error control of secondary endpoints in which certain protocol deviations occurred. We conducted an end of review (Type A) meeting at which the FDA reiterated, as stated in the CRL, that pimavanserin should be studied by individual subgroups of DRP, and advised us that the best path forward is to conduct an additional clinical study in each of the subgroups for which we seek approval. However, the FDA was also open to reviewing additional analyses from the HARMONY and -019 studies in support of a potential resubmission for individual subgroups without additional clinical studies. We subsequently held additional meetings (Type B) with the FDA and further discussed the potential for a resubmission based on additional analyses supporting a potential label for ADP specifically. In February 2022, we submitted to the FDA an sNDA for NUPLAZID for the treatment of hallucinations and delusions associated with ADP.

We are currently conducting several studies and may conduct additional studies in the future.

In connection with clinical trials, we face risks that:

- a product candidate may not prove to be efficacious or safe;
- patients may die or suffer other adverse effects for reasons that may or may not be related to the product candidate being tested;
- the results may not be consistent with positive results of earlier trials; and
- the results may not meet the level of statistical significance required by the FDA or other regulatory agencies.

If we do not successfully complete preclinical and clinical development, we will be unable to market and sell products derived from our product candidates and to generate product revenues. Even if we do successfully complete clinical trials, those results are not necessarily predictive of results of additional trials that may be needed before an NDA may be submitted to the FDA. Of the large number of drugs in development, only a small percentage result in the submission of an NDA to the FDA and even fewer are approved for commercialization.

Delays, suspensions and terminations in our clinical trials could result in increased costs to us and delay our ability to generate product revenues.

The commencement of clinical trials can be delayed for a variety of reasons, including delays in:

- demonstrating sufficient safety and efficacy to obtain regulatory approval to commence a clinical trial;
- reaching agreement on acceptable terms with prospective contract research organizations and clinical trial sites;
- manufacturing sufficient quantities of a product candidate;
- obtaining clearance from the FDA to commence clinical trials pursuant to an Investigational New Drug application;
- obtaining institutional review board approval to conduct a clinical trial at a prospective clinical trial site; and
- patient recruitment, which is a function of many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical trial sites, the availability of effective treatments for the relevant disease and the eligibility criteria for the clinical trial.

Once a clinical trial has begun, it may be delayed, suspended or terminated due to a number of factors, including:

- competition for internal and external resources, including clinical sites and study patients, that we may choose to allocate to other programs;
- ongoing discussions with regulatory authorities regarding the scope or design of our clinical trials or requests by them for supplemental information with respect to our clinical trial results;
- imposition of clinical holds by regulatory authorities or institutional review boards;
- failure to conduct clinical trials in accordance with regulatory requirements;
- patient enrollment, which is a function of many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical trial sites, the availability of effective treatments for the relevant disease and the eligibility criteria for the clinical trial;
- lower than anticipated screening or retention rates of patients in clinical trials;
- serious adverse events or side effects experienced by participants; and
- insufficient supply or deficient quality of product candidates or other materials necessary for the conduct of our clinical trials.

In addition, enrollment and retention of patients in clinical trials could be disrupted by man-made or natural disasters or public health emergencies. For example, as a result of the COVID-19 pandemic, we temporarily paused enrollment of new patients in our ongoing clinical trials, as well as commencement of new trials. However, we have re-initiated enrollment in clinical trials on a study-by-study and site-by-site basis. It is possible that future enrollment in these studies, or enrollment in future studies, could be impacted due to COVID-19. If patients withdraw from our trials, miss scheduled doses or follow-up visits or otherwise fail to follow trial protocols, or if our trial results are otherwise disputed due to COVID-19 or actions taken to slow its spread, the integrity of data from our trials may be compromised or not accepted by the FDA or other regulatory authorities, which would represent a significant setback for the applicable program.

Many of these factors may also ultimately lead to denial of regulatory approval of a current or potential product candidate. If we experience delays, suspensions or terminations in a clinical trial, the commercial prospects for the related product candidate will be harmed, and our ability to generate product revenues will be delayed.

If we are unable to attract, retain, and motivate key management, research and development, and sales and marketing personnel, our drug development programs, our research and discovery efforts, and our commercialization plans may be delayed and we may be unable to successfully commercialize our products, including NUPLAZID, or develop our product candidates, including pimavanserin for indications beyond PDP.

Our success depends on our ability to attract, retain, and motivate highly qualified management, scientific, and commercial personnel. In particular, our development programs depend on our ability to attract and retain highly skilled development personnel, especially in the fields of central nervous system disorders, including neuropsychiatric and related

disorders. We are currently hiring, and in the future we expect to need to continue to hire, additional personnel as we expand our research and development efforts for pimavanserin and commercial activities for NUPLAZID. We face competition for experienced scientists, clinical operations personnel, commercial and other personnel from numerous companies and academic and other research institutions. Competition for qualified personnel is particularly intense in the San Diego, California area. Many of the other biotechnology and pharmaceutical companies with whom we compete for qualified personnel have greater financial and other resources, different risk profiles and longer histories in the industry than we do. They also may provide more diverse opportunities and better chances for career advancement. Some of these characteristics may be more appealing to high quality candidates than that which we have to offer. If we are unable to continue to attract and retain high quality personnel, the rate and success at which we can develop and commercialize products and product candidates will be limited. If we are unable to attract and retain the necessary personnel, it will significantly impede our commercialization efforts for NUPLAZID and the achievement of our research and development objectives.

All of our employees are “at will” employees, which means that any employee may quit at any time and we may terminate any employee at any time. We do not carry “key person” insurance covering members of senior management.

If we receive approval of NUPLAZID in additional indications, including ADP, we would need to continue to increase the size of our organization. We may encounter difficulties with managing our growth, which could adversely affect our results of operations.

As of December 31, 2021, we employed approximately 510 employees. Our current infrastructure may be inadequate to support our development and commercialization efforts and expected growth. Future growth will impose significant added responsibilities on members of management, including the need to identify, recruit, and integrate additional employees and retain existing employees, and may take time away from running other aspects of our business, including development and commercialization of our product candidates.

Our future financial performance and our ability to commercialize NUPLAZID and any other product candidates that receive regulatory approval and to compete effectively will depend, in part, on our ability to manage any future growth effectively. In particular, as we commercialize NUPLAZID, we will need to support the training and ongoing activities of our sales force. To that end, we must be able to:

- manage our development efforts effectively;
- integrate additional management, administrative and manufacturing personnel;
- develop our marketing and sales organization; and
- maintain sufficient administrative, accounting and management information systems and controls.

We may not be able to accomplish these tasks or successfully manage our operations and, accordingly, may not achieve our research, development, and commercialization goals. Our failure to accomplish any of these goals could harm our financial results and prospects.

If we fail to develop, acquire or in-license other product candidates or products, our business and prospects would be limited. Even if we obtain rights to other product candidates or products, we will incur a variety of costs and may never realize the anticipated benefits.

A key element of our strategy is to develop, acquire or in-license businesses, technologies, product candidates or products that we believe are a strategic fit with our business. The success of this strategy depends in large part on the combination of our regulatory, development and commercial capabilities and expertise and our ability to identify, select and acquire or in-license clinically-enabled product candidates for the treatment of neurological disorders, or for therapeutic indications that complement or augment our current product candidates, or that otherwise fit into our development or strategic plans on terms that are acceptable to us. Identifying, selecting and acquiring or in-licensing promising product candidates requires substantial technical, financial and human resources expertise, and we have limited experience in identifying acquisition targets, successfully completing proposed acquisitions and integrating any acquired businesses, technologies, services or products into our current infrastructure. Efforts to do so may not result in the actual acquisition or in-license of a particular product candidate, potentially resulting in a diversion of our management’s time and the expenditure of our resources with no resulting benefit. If we are unable to identify, select and acquire or license suitable product candidates from third parties on terms acceptable to us, our business and prospects will be limited. In particular, if we are unable to add additional commercial products to our portfolio, we may not be able to successfully leverage our commercial organization that we have assembled for the marketing and sale of NUPLAZID.

The process of integrating any acquired business, technology, service, or product may result in unforeseen operating difficulties and expenditures and may divert significant management attention from our ongoing business operations. As a result, we will incur a variety of costs in connection with an acquisition and may never realize its anticipated benefits. Moreover, any product candidate we identify, select and acquire or license may require additional, time-consuming development or regulatory efforts prior to commercial sale, including preclinical studies, if applicable, and extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All product candidates are prone to the risk of failure that is inherent in pharmaceutical product development, including the possibility that the product candidate will not be shown to be sufficiently safe and/or effective for approval by regulatory authorities. In addition, we cannot assure you that any such products that are approved will be manufactured or produced economically, successfully commercialized or widely accepted in the marketplace or be more effective or desired than other commercially available alternatives.

In addition, if we fail to successfully commercialize and further develop NUPLAZID or our product candidates, there is a greater likelihood that we will fail to successfully develop a pipeline of other product candidates, and our business and prospects would therefore be harmed.

We expect our net losses to continue for the next few years and are unable to predict the extent of future losses or when we will become profitable, if ever.

We have experienced significant net losses since our inception. As of December 31, 2021, we had an accumulated deficit of approximately $2.2 billion. We expect to incur net losses over the next few years as we invest in the commercialization of NUPLAZID and advance our development programs.

Even though we began commercializing NUPLAZID in the U.S. in May 2016, we still expect to incur significant expenses and net losses for at least the next few years as we continue our commercialization efforts for NUPLAZID and pursue the further development of NUPLAZID and our product candidates. Substantially all of our revenues since May 2016 were from net product sales of NUPLAZID.

We expect that our revenues over the next few years will be entirely dependent on our ability to generate net product sales of NUPLAZID. To the extent that we cannot generate significant revenues from the sale of NUPLAZID to cover our expenses, including the significant expenses associated with commercializing NUPLAZID and continuing to develop pimavanserin in additional indications, we may never achieve profitability and/or may have to reduce our commercialization and/or research and development activities to become profitable, which would harm our future growth prospects. Additionally, to obtain revenues from product candidates other than NUPLAZID, we must succeed, either alone or with others, in developing, obtaining regulatory approval for, manufacturing and marketing compounds with significant market potential. We may never succeed in these activities and may never generate revenues from our commercialization of NUPLAZID, or from other product candidates that may be approved, that are significant enough to achieve profitability.

If we fail to obtain the capital necessary to fund our operations, we will be unable to successfully continue the development and commercialization of NUPLAZID or successfully develop and commercialize our other product candidate opportunities.

We have consumed substantial amounts of capital since our inception. Our cash, cash equivalents, and investment securities totaled $520.7 million at December 31, 2021. While we believe that our existing cash resources will be sufficient to fund our cash requirements through at least the next twelve months, we may require significant additional financing in the future to continue to fund our operations. Our future capital requirements will depend on, and could increase significantly as a result of, many factors including:

- the progress in, and the costs of, our ongoing and planned development activities for pimavanserin, post-marketing studies for NUPLAZID to be conducted over the next several years, ongoing and planned commercial activities for NUPLAZID, and other research and development programs;
- the costs of our development activities for trofinetide, ACP-044, ACP-319 and the M1 PAM program and any other product candidates;
- the costs of commercializing NUPLAZID, including the maintenance and development of our sales and marketing capabilities;
- the costs of establishing, or contracting for, sales and marketing capabilities for other product candidates;
- the amount of U.S. product sales from NUPLAZID;

- the costs of preparing applications for regulatory approvals for NUPLAZID in jurisdictions other than the U.S., and in additional indications other than in PDP, and for other product candidates, as well as the costs required to support review of such applications;
- the costs of manufacturing and distributing NUPLAZID for commercial use in the U.S.;
- our ability to obtain regulatory approval for, and subsequently generate product sales from, NUPLAZID in jurisdictions other than the U.S. or in additional indications other than in PDP, or from trofinetide, ACP-044, ACP-319 and the M1 PAM program and any other product candidates;
- the costs of acquiring additional product candidates or research and development programs;
- the scope, prioritization and number of our research and development programs;
- the ability of our collaborators and us to reach the milestones and other events or developments triggering payments under our collaboration or license agreements, or our collaborators' ability to make payments under these agreements;
- our ability to enter into new collaboration and license agreements;
- the extent to which we are obligated to reimburse collaborators or collaborators are obligated to reimburse us for costs under collaboration agreements;
- the costs involved in filing, prosecuting, enforcing, and defending patent claims and other intellectual property rights;
- the costs of maintaining or securing manufacturing arrangements and supply for clinical or commercial production of pimavanserin, trofinetide or other product candidates; and
- the costs associated with litigation, including the costs incurred in defending against any product liability claims that may be brought against us related to NUPLAZID.

Unless and until we can generate significant cash from our operations, we expect to satisfy our future cash needs through our existing cash, cash equivalents and investment securities, strategic collaborations, public or private sales of our securities, debt financings, grant funding, or by licensing all or a portion of our product candidates or technology. In the past, periods of turmoil and volatility in the financial markets have adversely affected the market capitalizations of many biotechnology companies, and generally made equity and debt financing more difficult to obtain. For example, as a result of the COVID-19 pandemic and actions taken to slow its spread, the global credit and financial markets have experienced extreme volatility and disruptions, including diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. These events, coupled with other factors, may limit our access to additional financing in the future. This could have a material adverse effect on our ability to access sufficient funding. We cannot be certain that additional funding will be available to us on acceptable terms, or at all. If funds are not available, we will be required to delay, reduce the scope of, or eliminate one or more of our research or development programs or our commercialization efforts. We also may be required to relinquish greater or all rights to product candidates at an earlier stage of development or on less favorable terms than we would otherwise choose. Additional funding, if obtained, may significantly dilute existing stockholders and could negatively impact the price of our stock.

We expect that our results of operations will fluctuate, which may make it difficult to predict our future performance from period to period.

Our operating results have fluctuated in the past and are likely to do so in future periods. Some of the factors that could cause our operating results to fluctuate from period to period include:

- the success of our commercialization of NUPLAZID in the U.S. for the treatment of hallucinations and delusions associated with PDP;
- the impact of the COVID-19 pandemic on our business, including the ability of our field sales force to meet with healthcare providers, visit physician's offices, hospitals and other healthcare facilities (including long-term care and skilled nursing facilities);
- the status and cost of our post-marketing commitments for NUPLAZID;

- the variation in our gross-to-net adjustments from quarter to quarter, primarily because of the fluctuation in our share of the donut hole for Medicare Part D patients;
- the status and cost of development and commercialization of pimavanserin for indications other than in PDP and in jurisdictions other than the U.S.;
- the status and cost of development and commercialization of our product candidates, including compounds being developed under our collaborations;
- whether we acquire or in-license additional product candidates or products, and the status of development and commercialization of such product candidates or products;
- whether we generate revenues or reimbursements by achieving specified research, development or commercialization milestones under any agreements or otherwise receive potential payments under these agreements;
- whether we are required to make payments due to achieving specified milestones under any licensing or similar agreements or otherwise make payments under these agreements;
- the incurrence of preclinical or clinical expenses that could fluctuate significantly from period to period, including reimbursement obligations pursuant to our collaboration agreements;
- the initiation, termination, or reduction in the scope of our collaborations or any disputes regarding these collaborations;
- the timing of our satisfaction of applicable regulatory requirements;
- the rate of expansion of our clinical development, other internal research and development efforts, and pre-commercial and commercial efforts;
- the effect of competing technologies and products and market developments;
- the costs associated with litigation, including the costs incurred in defending against any product liability claims that may be brought against us related to NUPLAZID; and
- general and industry-specific economic conditions.

We believe that comparisons from period to period of our financial results are not necessarily meaningful and should not be relied upon as indications of our future performance.

From time to time, we provide guidance relating to our expectations for NUPLAZID net sales and certain expense line items based on estimates and the judgment of management. If, for any reason, our actual net sales or expenses differ materially from our guidance, we may have to revise our previously announced financial guidance. If we change, update or fail to meet any element of such guidance, our stock price could decline.

Changes in tax laws or regulations that are applied adversely to us or our customers may have a material adverse effect on our business, cash flow, financial condition or results of operations.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the Biden administration and Congress have proposed various U.S. federal tax law changes, which if enacted could have a material impact on our business, cash flows, financial condition, or results of operations. In addition, it is uncertain if and to what extent various states will conform to federal tax laws. Future tax reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges, and could increase our future U.S. tax expense.

Our ability to use net operating losses and certain other tax attributes to offset future taxable income or taxes may be limited.

Portions of our net operating loss carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under current law, federal net operating losses incurred in tax years beginning after December 31, 2017, may be carried forward indefinitely, but the deductibility of such federal net operating losses in tax years beginning after December 31, 2020, is limited to 80% of taxable income. It is uncertain if and to what extent various states will conform to federal tax laws. In addition, under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (the Code), and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50 percent change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. We have experienced ownership changes in the past and we may experience additional ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our net operating loss carryforwards is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. In addition, at the state level, there may be periods during which the use of net operating loss carryforwards is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed. As a result, if we earn net taxable income, we may be unable to use all or a material portion of our net operating loss carryforwards and other tax attributes, which could potentially result in increased future tax liability to us and adversely affect our future cash flows.

Tax authorities could reallocate our taxable income among out subsidiaries, which could increase our overall tax liability.

In 2015, we licensed worldwide intellectual property rights related to pimavanserin in certain indications to Acadia Pharmaceuticals GmbH, our wholly owned Swiss subsidiary (Acadia GmbH), and in July 2020 we licensed additional related rights to Acadia GmbH. Our goals for the establishment of Acadia GmbH, and the licensing of worldwide intellectual property rights for pimavanserin, include building a platform for long-term operational and financial efficiencies, including tax-related efficiencies. Future changes in U.S. and non-U.S. tax laws, including implementation of international tax reform relating to the tax treatment of multinational corporations, if enacted, may reduce or eliminate any potential financial efficiencies that we hoped to achieve by establishing this operational structure. Additionally, taxing authorities, such as the U.S. Internal Revenue Service, may audit and otherwise challenge these types of arrangements, and have done so with other companies in the pharmaceutical industry. If any such changes in tax law are enacted, or our licensing of worldwide intellectual property rights for pimavanserin to our Swiss subsidiary is otherwise challenged, this could materially adversely affect our business.

Public health threats, including the continuing COVID-19 pandemic, have impacted our clinical trials and could have an adverse effect on our operations and financial results, or may cause us to modify or suspend our financial guidance.

On March 11, 2020, the World Health Organization declared a pandemic resulting from the disease known as COVID-19 caused by a novel strain of coronavirus, SARS-CoV-2. The rapid global spread of COVID-19 has had a major impact on the financial markets, the global economy and the economies of particular countries or regions, and led to travel restrictions, quarantines, "work-at-home" and "shelter-in-place" orders imposed by authorities and the extended shutdown of certain non-essential businesses in the U.S. throughout the world, including in countries where we have planned or active clinical trials. In an effort to protect the health and safety of our employees and our stakeholders, we adopted recommended policies applicable to office-based employees such as working from home, limiting the number of employees on site, and limiting business travel. For our field-based commercial and medical affairs personnel, we have instituted a protocol to assess the safety of employees to conduct in-person interactions on a localized basis in accordance with applicable regulatory guidance and local policies. We continue to closely monitor the COVID-19 situation and will reopen our offices to allow employees to return when appropriate. We may face several challenges or disruptions upon a return back to the workplace, including re-integration challenges by our employees and distractions to management related to such transition. The effects and duration of such measures could have a material adverse impact on our business, results of operations, financial condition and prospects.

Our sales force has had physical access to hospitals, clinics, long-term care and skilled nursing facilities, healthcare providers and pharmacies curtailed, which may have a material adverse effect on our future sales. Currently, health care providers are conducting patient visits in-person and through telemedicine and our sales force has been able to call upon medical clinics, hospitals, long-term care facilities and skilled nursing facilities either in person in accordance with applicable regulatory guidance and local policies or virtually. While digital tools are available to our field employees to facilitate remote meetings with healthcare providers that are unable to meet in-person, we cannot ensure that these methods will be effective. Additionally, patients who are currently using NUPLAZID or who are eligible to use NUPLAZID, may be unable to meet with their healthcare providers in person, which may reduce the number of prescription refills or new patient starts, affecting our revenues both in our currently approved indication and potentially impacting our anticipated launches in other indications, if approved.

Our clinical trials have been impacted by the COVID-19 pandemic. We temporarily paused enrollment of new patients in our ongoing clinical trials as well as commencement of new trials, and our data collection and site monitoring activities relating to currently active clinical trials could be delayed or otherwise impeded by travel and access restrictions and diversion of healthcare resources toward treating COVID-19 patients, among other things. However, we have re-initiated enrollment in clinical trials on a study-by-study and site-by-site basis. It is possible that future enrollment in these studies, or enrollment in future studies, could be impacted due to COVID-19.

During 2021, sales of NUPLAZID were negatively impacted by ongoing conditions related to the pandemic, including a reduction in patient office visits and a continuing reduced occupancy rates at long-term care facilities. While we observed incremental improvements in some of these factors during the latter part of the year, their levels are still meaningfully below where they were pre-pandemic. It remains difficult to predict the duration of the pandemic's impact and the pace of, and no assurances can be given that the pandemic will not continue to have additional negative impacts on our business, results of operations, financial condition and prospects.

Earthquake or fire damage to our facilities could delay our research and development efforts and adversely affect our business.

Our headquarters and research and development facilities in San Diego are located in a seismic zone, and there is the possibility of an earthquake, which could be disruptive to our operations and result in delays in our research and development efforts. In addition, while our facilities have not been adversely impacted by local wildfires, there is the possibility of future fires in the area. In the event of an earthquake or fire, if our facilities or the equipment in our facilities is significantly damaged or destroyed for any reason, we may not be able to rebuild or relocate our facilities or replace any damaged equipment in a timely manner and our business, financial condition, and results of operations could be materially and adversely affected. We do not have insurance for damages resulting from earthquakes. While we do have fire insurance for our property and equipment located in San Diego, any damage sustained in a fire could cause a delay in our research and development efforts and our results of operations could be materially and adversely affected.

Our business involves the use of hazardous materials, and we and our third-party manufacturers and suppliers must comply with environmental, health and safety laws and regulations, which can be expensive and restrict how we do, or interrupt our, business.

Our research and development activities and our third-party manufacturers' and suppliers' activities involve the generation, storage, use and disposal of hazardous materials, including the components of our products and product candidates and other hazardous compounds and wastes. We and our manufacturers and suppliers are subject to environmental, health and safety laws and regulations governing, among other matters, the use, manufacture, generation, storage, handling, transportation, discharge and disposal of these hazardous materials and wastes and worker health and safety. In some cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination or injury, which could result in an interruption of our commercialization efforts, research and development efforts and business operations, damages and significant cleanup costs and liabilities under applicable environmental, health and safety laws and regulations. We also cannot guarantee that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials and wastes generally comply with the standards prescribed by these laws and regulations. We may be held liable for any resulting damages costs or liabilities, which could exceed our resources, and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental, health and safety laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. Failure to comply with these

environmental, health and safety laws and regulations may result in substantial fines, penalties or other sanctions. We do not currently carry hazardous waste insurance coverage.

Risks Related to Our Relationships with Third Parties

We previously have depended, and in the future may depend, on collaborations with third parties to develop and commercialize selected product candidates other than pimavanserin, and we have limited control over how those third parties conduct development and commercialization activities for such product candidates.

In the past, we have selectively entered into collaboration agreements with third parties. We relied on our collaborators for financial resources and for development, regulatory, and commercialization expertise for selected product candidates and we had limited control over the amount and timing of resources that our collaborators devoted to our product candidates. We may choose to rely on collaborations in the future for certain portions of our pimavanserin program or other product candidates, or for the commercialization of NUPLAZID in certain territories outside of the U.S.

Our collaborators may fail to develop or effectively commercialize products using our product candidates or technologies because they:

- do not have sufficient resources or decide not to devote the necessary resources due to internal constraints such as limited cash or human resources or a change in strategic focus;
- decide to pursue a competitive product developed outside of the collaboration; or
- cannot obtain the necessary regulatory approvals.

We also face competition in our search for new collaborators, if we seek a new partner for our pimavanserin program or other programs. Given the current economic and industry environment, it is possible that competition for new collaborators may increase. If we are unable to find new collaborations, we may not be able to continue advancing our programs alone.

If conflicts arise with our collaborators, they may act in their self-interests, which may be adverse to our interests.

Conflicts may arise in our collaborations due to one or more of the following:

- disputes or breaches with respect to payments that we believe are due under the applicable agreements, particularly in the current environment when companies, including large established ones, may be seeking to reduce external payments;
- disputes on strategy as to what development or commercialization activities should be pursued under the applicable agreements;
- disputes as to the responsibility for conducting development and commercialization activities pursuant to the applicable collaboration, including the payment of costs related thereto;
- disagreements with respect to ownership of intellectual property rights;
- unwillingness on the part of a collaborator to keep us informed regarding the progress of its development and commercialization activities, or to permit public disclosure of these activities;
- delay or reduction of a collaborator’s development or commercialization efforts with respect to our product candidates; or
- termination or non-renewal of the collaboration.

Conflicts arising with our collaborators could impair the progress of our product candidates, harm our reputation, result in a loss of revenues, reduce our cash position, and cause a decline in our stock price.

In addition, in our past collaborations, we generally have agreed not to conduct independently, or with any third party, any research that is directly competitive with the research conducted under the applicable program. Any collaborations we establish in the future may have the effect of limiting the areas of research that we may pursue, either alone or with others. Conversely, the terms of any collaboration we may establish in the future might not restrict our collaborators from developing, either alone or with others, products in related fields that are competitive with the products or potential products

that are the subject of these collaborations. Competing products, either developed by our collaborators or to which our collaborators have rights, may result in the allocation of resources by our collaborators to competing products and their withdrawal of support for our product candidates or may otherwise result in lower demand for our potential products.

We rely on third parties to conduct our clinical trials and perform data collection and analysis, which may result in costs and delays that prevent us from successfully commercializing product candidates.

Although we design and manage our current preclinical studies and clinical trials, we currently do not have the ability to conduct clinical trials for our product candidates on our own. We rely on contract research organizations, medical institutions, clinical investigators, and contract laboratories to perform data collection and analysis and other aspects of our clinical trials. In addition, we also rely on third parties to assist with our preclinical studies, including studies regarding biological activity, safety, absorption, metabolism, and excretion of product candidates. Some of these third parties may experience shutdowns or other disruptions as a result of the COVID-19 pandemic and therefore may be unable to provide the level of service that we have received in the past.

Our preclinical activities or clinical trials may be delayed, suspended, or terminated if:

- these third parties do not successfully carry out their contractual duties or fail to meet regulatory obligations or expected deadlines;
- these third parties need to be replaced; or
- the quality or accuracy of the data obtained by these third parties is compromised due to their failure to adhere to our clinical protocols or regulatory requirements or for other reasons.

Failure to perform by these third parties may increase our development costs, delay our ability to obtain regulatory approval, and delay or prevent the commercialization of our product candidates. We currently use several contract research organizations to perform services for our preclinical studies and clinical trials. While we believe that there are numerous alternative sources to provide these services, in the event that we seek such alternative sources, we may not be able to enter into replacement arrangements without delays or additional expenditures.

Even if we or our collaborators successfully complete the clinical trials of product candidates, the product candidates may fail for other reasons.

Of the large number of product candidates in development, only a small percentage result in the submission of an NDA to the FDA or comparable regulatory filing to regulatory authorities in other jurisdictions, and even fewer are approved for marketing. We cannot assure you that, even if clinical trials are completed, either we or our collaborators will submit applications for required authorizations to manufacture and/or market potential products or that any such application will be reviewed and approved by the appropriate regulatory authorities in a timely manner, if at all. Even if we or our collaborators successfully complete the clinical trials of product candidates and apply for such required authorizations, the product candidates, such as pimavanserin, may fail for other reasons, including the possibility that the product candidates will:

- fail to receive the regulatory clearances required to market them as drugs;
- be subject to proprietary rights held by others requiring the negotiation of a license agreement prior to marketing;
- be difficult or expensive to manufacture on a commercial scale;
- have adverse side effects that make their use less desirable; or
- fail to compete with product candidates or other treatments commercialized by competitors.

We currently depend, and in the future will continue to depend, on third parties to manufacture NUPLAZID, trofinetide and any other product candidates. If these manufacturers fail to provide us or our collaborators with adequate supplies of clinical trial materials and commercial product or fail to comply with the requirements of regulatory authorities, we may be unable to develop or commercialize NUPLAZID, trofinetide or any other product candidates.

We have no manufacturing facilities and only limited experience as an organization in the manufacturing of drugs or in designing drug-manufacturing processes. We have contracted with third-party manufacturers to produce, in collaboration with us, NUPLAZID and our product candidates.

We have contracted with Patheon Pharmaceuticals Inc. to manufacture NUPLAZID 10 mg tablet and 34 mg capsule drug product for commercial use in the U.S. We have also contracted with a second contract manufacturing organization to manufacture NUPLAZID 34 mg drug product for commercial use in the U.S. Additionally, we have contracted with Siegfried AG to manufacture active pharmaceutical ingredient (API), to be used in the manufacture of NUPLAZID drug product for commercial use. However, we have not entered into any agreements with any alternate suppliers for 10 mg NUPLAZID drug product or NUPLAZID API, and we may face delays or increased costs in our supply chain that could jeopardize the commercialization of NUPLAZID. While we currently have sufficient API and NUPLAZID finished product on hand to continue our commercial and clinical operations as planned, depending on the length of the COVID-19 pandemic and whether further disruptions occur, we may face such delays or costs in future years. If any third party in our supply or distribution chain for materials or finished product is adversely impacted by restrictions resulting from the COVID-19 outbreak, including staffing shortages, production slowdowns and disruptions in delivery systems, our supply chain may be disrupted, limiting our ability to manufacture and distribute NUPLAZID for commercial sales and our product candidates for our clinical trials and research and development operations. Additionally, if NUPLAZID is approved for commercial sale in jurisdictions outside the U.S., we will need to contract with a third party to manufacture such products for commercial sale in the U.S. and/or in such other jurisdictions.

We have contracted with manufacturers to produce clinical supplies of trofinetide to support the development program. If trofinetide or any other product candidate is approved by the FDA or other regulatory agencies for commercial sale, we will need to contract with a third party to manufacture such products for commercial sale in the U.S. and/or in such other jurisdictions.

Even though we have agreements with Patheon for the manufacture of NUPLAZID 10 mg tablet and agreements with Patheon and another manufacturer for the manufacture of 34 mg capsule drug product, and with Siegfried for the manufacture of NUPLAZID API for commercial use, and even if we successfully enter into long-term agreements with other manufacturers, the FDA may not approve the facilities of such manufacturers, the manufacturers may not perform as agreed, or the manufacturers may terminate their agreements with us. Presently, we have only one supplier of API, two suppliers for the 34 mg capsule and one supplier for the 10mg tablet of NUPLAZID. If any of the foregoing circumstances occur, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, maintain or obtain, as applicable, regulatory approval for or market NUPLAZID or trofinetide or any other product candidates. While we believe that there will be alternative sources available to manufacture NUPLAZID and trofinetide and any other product candidates, in the event that we seek such alternative sources, we may not be able to enter into replacement arrangements without delays or additional expenditures. We cannot estimate these delays or costs with certainty but, if they were to occur, they could cause a delay in our development and commercialization efforts.

The manufacturers of NUPLAZID and trofinetide and any other product candidates, including Patheon and Siegfried, are obliged to operate in accordance with FDA-mandated current good manufacturing practices (cGMPs), and we have limited control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance and qualified personnel to ensure compliance with cGMPs. In addition, the facilities used by our third-party manufacturers to manufacture NUPLAZID and trofinetide and any other product candidates must be approved by the FDA pursuant to inspections that will be conducted prior to any grant of regulatory approval by the FDA. If any of our third-party manufacturers are unable to successfully manufacture material that conforms to our specifications and the FDA's strict regulatory requirements, or pass regulatory inspection, they will not be able to secure or maintain approval for the manufacturing facilities. Additionally, a failure by any of our third-party manufacturers to establish and follow cGMPs or to document their adherence to such practices may lead to significant delays in clinical trials or in obtaining regulatory approval of product candidates, or result in issues maintaining regulatory approval of NUPLAZID and trofinetide and any other product candidate that receives regulatory approval, negatively impact our commercialization of NUPLAZID, or lead to significant delays in the launch and commercialization of trofinetide or any other products we may have in the future. Failure by our third-party manufacturers or us to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, failure of the government to grant pre-market approval of drugs, delays, suspension or withdrawal of approvals, seizures or recalls of products, operating restrictions, and criminal prosecutions.

The manufacture of pharmaceutical products requires significant capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production. These problems include difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. We cannot assure you that any issues relating to the manufacture of NUPLAZID or trofinetide or any other product candidates will not occur in the future. Additionally, our manufacturers may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If our manufacturers were to encounter any of these difficulties, or otherwise fail to comply with their contractual obligations, our ability to commercialize NUPLAZID in the U.S., or provide trofinetide or any other product candidates to patients in clinical trials, would be jeopardized. Any delay or interruption in our ability to meet commercial demand for NUPLAZID and any other approved products will result in the loss of potential revenues and could adversely affect our ability to gain market acceptance for these products. In addition, any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, increase the costs associated with maintaining clinical trial programs and, depending upon the period of delay, require us to commence new clinical trials at additional expense or terminate clinical trials completely.

Failures or difficulties faced at any level of our supply chain could materially adversely affect our business and delay or impede the development and commercialization of NUPLAZID or trofinetide or any other product candidates and could have a material adverse effect on our business, results of operations, financial condition and prospects.

If we fail to comply with the obligations in agreements under which we license intellectual property rights from third parties, we could lose license rights to certain of our product candidates.

In August 2018, we entered into a license agreement with Neuren, and obtained exclusive North American rights to develop and commercialize trofinetide for Rett syndrome and other indications. In March 2020, we entered into a license agreement with Vanderbilt University, and obtained exclusive worldwide license to develop and commercialize our M1 PAM program, and we may enter into additional license agreements in the future. In January 2022, we entered into a license and collaboration agreement with Stoke to discover, develop and commercialize novel RNA-based medicines for the potential treatment of severe and rare genetic neurodevelopmental diseases of the CNS.

Our agreements with Neuren, Vanderbilt University and Stoke impose, and we expect that future agreements where we in-license intellectual property will impose, various development, regulatory and/or commercial diligence obligations, payment of milestones and/or royalties and other obligations. If we fail to comply with our obligations under these agreements, or we are subject to bankruptcy-related proceedings, the licensor may have the right to terminate the license, in which event we would not be able to market products covered by the license.

Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patents and other rights to third parties;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations;
- our right to transfer or assign the license; and
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may not be able to successfully develop and commercialize the related product candidates, which would have a material adverse effect on our business.

We may not be able to continue or fully exploit our collaborations with outside scientific and clinical advisors, which could impair the progress of our clinical trials and our research and development efforts.

We work with scientific and clinical advisors at academic and other institutions who are experts in the field of central nervous system disorders. They assist us in our research and development efforts and advise us with respect to our clinical trials. These advisors are not our employees and may have other commitments that would limit their future availability to us. Although our scientific and clinical advisors generally agree not to engage in competing work, if a conflict of interest arises between their work for us and their work for another entity, we may lose their services, which may impair our reputation in the industry and delay the development or commercialization of our product candidates.

Risks Related to Our Intellectual Property

Our ability to compete may decline if we do not adequately protect our proprietary rights.

Our commercial success depends on obtaining and maintaining intellectual property rights to our products and product candidates, including NUPLAZID, and technologies, as well as successfully defending these rights against third-party challenges. Successful challenges to, or misappropriation of, our intellectual property could enable competitors to quickly duplicate or surpass our technological achievements, thus eroding our competitive position in our market. To protect our intellectual property, we rely on a combination of patents, trade secret protection and contracts requiring confidentiality and nondisclosure. If our patents are successfully challenged, we may face generic competition prior to the expiration dates of our U.S. Orange Book listed patents. In addition, potential competitors have in the past and may in the future file an Abbreviated New Drug Application (ANDA) with the FDA for generic versions of NUPLAZID, seeking approval prior to the expiration of our patents. In response, we have filed complaints against these companies alleging infringement of certain of our Orange Book-listed patents covering NUPLAZID. For a more detailed description of these matters, see section captioned “Legal Proceedings” elsewhere in this report. While we intend to defend the validity of such patents vigorously, and will seek to use all appropriate methods to prevent their infringement, such efforts are expensive and time consuming. Any substantial decrease in the revenue and income derived from NUPLAZID would have an adverse effect on our results of operations.

With regard to patents, although we have filed numerous patent applications worldwide with respect to pimavanserin, not all of our patent applications resulted in an issued patent, or they resulted in an issued patent that is susceptible to challenge by a third party. Our ability to obtain, maintain, and/or defend our patents covering our product candidates and technologies is uncertain due to a number of factors, including:

- we may not have been the first to make the inventions covered by our pending patent applications or issued patents;
- we may not have been the first to file patent applications for our product candidates or the technologies we rely upon;
- others may develop similar or alternative technologies or design around our patent claims to produce competitive products that fall outside of the scope of our patents;
- our disclosures in patent applications may not be sufficient to meet the statutory requirements for patentability;
- we may not seek or obtain patent protection in all countries that will eventually provide a significant business opportunity;
- any patents issued to us or our collaborators may not provide a basis for commercially viable products, may not provide us with any competitive advantages, or are easily susceptible to challenges by third parties;
- our proprietary technologies may not be patentable;
- changes to patent laws that limit the exclusivity rights of patent holders or make it easier to render a patent invalid;
- recent decisions by the U.S. Supreme Court limiting patent-eligible subject matter;
- litigation regarding our patents may include challenges to the validity, enforceability, scope and term of one or more patents;
- the passage of The Leahy-Smith America Invents Act (the America Invents Act), introduced new procedures for challenging pending patent applications and issued patents; and

- technology that we may in-license may become important to some aspects of our business, however, we generally would not control the patent prosecution, maintenance or enforcement of any such in-licensed technology.

Even if we have or obtain patents covering our product candidates or technologies, we may still be barred from making, using and selling our product candidates or technologies because of the patent rights of others. Others have or may have filed, and in the future are likely to file, patent applications covering compounds, assays, genes, gene products or therapeutic products that are similar or identical to ours. There are many issued U.S. and foreign patents relating to genes, nucleic acids, polypeptides, chemical compounds or therapeutic products, and some of these may encompass reagents utilized in the identification of candidate drug compounds or compounds that we desire to commercialize. Numerous U.S. and foreign issued patents and pending patent applications owned by others exist in the area of central nervous system disorders and the other fields in which we are developing products. These could materially affect our freedom to operate. Moreover, because patent applications can take many years to issue, there may be currently pending applications, unknown to us, that may later result in issued patents that our product candidates or technologies may infringe. These patent applications may have priority over patent applications filed by us.

We regularly conduct searches to identify patents or patent applications that may prevent us from obtaining patent protection for our proprietary compounds or that could limit the rights we have claimed in our patents and patent applications. Disputes may arise regarding the ownership or inventorship of our inventions. For applications in which all claims are entitled to a priority date before March 16, 2013, an interference proceeding can be provoked by a third-party or instituted by the U.S. Patent and Trademark Office (U.S. PTO), to determine who was the first to invent the invention at issue. It is difficult to determine how such disputes would be resolved. Applications containing a claim not entitled to priority before March 16, 2013, are not subject to interference proceedings due the change brought by the America Invents Act to a “first-to-file” system. However, a derivation proceeding can be brought by a third-party alleging that the inventor derived the invention from another.

Periodic maintenance fees on any issued patent are due to be paid to the U.S. PTO and foreign patent agencies in several stages over the lifetime of the patent. The U.S. PTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, 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. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. In such an event, our competitors might be able to enter the market, which would have a material adverse effect on our business.

Some of our academic institutional licensors, research collaborators and scientific advisors have rights to publish data and information to which we have rights. We generally seek to prevent our collaborators from disclosing scientific discoveries until we have the opportunity to file patent applications on such discoveries, but in some cases, we are limited to relatively short periods to review a proposed publication and file a patent application. If we cannot maintain the confidentiality of our technology and other confidential information in connection with our collaborations, then our ability to receive patent protection or protect our proprietary information may be impaired.

Confidentiality agreements with employees and others may not adequately prevent disclosure of our trade secrets and other proprietary information and may not adequately protect our intellectual property, which could limit our ability to compete.

Because we operate in the highly technical field of drug discovery and development of small molecule drugs, we rely in part on trade secret protection in order to protect our proprietary technology and processes. However, trade secrets are difficult to protect. We enter into confidentiality, nondisclosure, and intellectual property assignment agreements with our corporate partners, employees, consultants, outside scientific collaborators, sponsored researchers, and other advisors. These agreements generally require that the other party keep confidential and not disclose to third parties all confidential information developed by the party or made known to the party by us during the course of the party’s relationship with us. These agreements also generally provide that inventions conceived by the party in the course of rendering services to us will be our exclusive property. However, these agreements may not be honored and may not effectively assign intellectual property rights to us. Enforcing a claim that a party illegally obtained and is using our trade secrets is difficult, expensive and time consuming and the outcome is unpredictable. In addition, courts outside the U.S. may be less willing to protect trade

secrets. We also have not entered into any noncompete agreements with any of our employees. Although each of our employees is required to sign a confidentiality agreement with us at the time of hire, we cannot guarantee that the confidential nature of our proprietary information will be maintained in the course of future employment with any of our competitors. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, we will not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, operating results and financial condition.

A dispute concerning the infringement or misappropriation of our proprietary rights or the proprietary rights of others could be time-consuming and costly, and an unfavorable outcome could harm our business.

There is a substantial amount of litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, as well as administrative proceedings for challenging patents, including post-issuance review proceedings before the U.S. PTO or oppositions and other comparable proceedings in foreign jurisdictions.

Central provisions of the America Invents Act went into effect on September 16, 2012 and on March 16, 2013. The America Invents Act includes a number of significant changes to U.S. patent law. These changes include provisions that affect the way patent applications are being filed, prosecuted and litigated. For example, the America Invents Act enacted proceedings involving post-issuance patent review procedures, such as inter partes review (IPR), and post-grant review, that allow third parties to challenge the validity of an issued patent in front of the U.S. PTO Patent Trial and Appeal Board. Each proceeding has different eligibility criteria and different patentability challenges that can be raised. IPRs permit any person (except a party who has been litigating the patent for more than a year) to challenge the validity of the patent on the grounds that it was anticipated or made obvious by prior art. Patents covering pharmaceutical products have been subject to attack in IPRs from generic drug companies and from hedge funds. If it is within nine months of the issuance of the challenged patent, a third party can petition the U.S. PTO for post-grant review, which can be based on any invalidity grounds and is not limited to prior art patents or printed publications.

In post-issuance proceedings, U.S. PTO rules and regulations generally tend to favor patent challengers over patent owners. For example, unlike in district court litigation, claims challenged in post-issuance proceedings are given their broadest reasonable meaning, which increases the chance a claim might be invalidated by prior art or lack support in the patent specification. As another example, unlike in district court litigation, there is no presumption of validity for an issued patent, and thus, a challenger's burden to prove invalidity is by a preponderance of the evidence, as opposed to the heightened clear and convincing evidence standard. As a result of these rules and others, statistics released by the U.S. PTO show a high percentage of claims being invalidated in post-issuance proceedings. Moreover, with few exceptions, there is no standing requirement to petition the U.S. PTO for inter partes review or post-grant review. In other words, companies that have not been charged with infringement or that lack commercial interest in the patented subject matter can still petition the U.S. PTO for review of an issued patent. Thus, even where we have issued patents, our rights under those patents may be challenged and ultimately not provide us with sufficient protection against competitive products or processes.

We may be exposed to future litigation by third parties based on claims that our product candidates, technologies or activities infringe the intellectual property rights of others. In particular, there are many patents relating to specific genes, nucleic acids, polypeptides or the uses thereof to identify product candidates. Some of these may encompass genes or polypeptides that we utilize in our drug development activities. If our drug development activities are found to infringe any such patents, and such patents are held to be valid and enforceable, we may have to pay significant damages or seek licenses to such patents. A patentee could prevent us from using the patented genes or polypeptides for the identification or development of drug compounds. There are also many patents relating to chemical compounds and the uses thereof. If our compounds are found to infringe any such patents, and such patents are held to be valid and enforceable, we may have to pay significant damages or seek licenses to such patents. A patentee could prevent us from making, using or selling the patented compounds.

In addition to the patent infringement lawsuits that we have recently initiated against the filers of ANDAs pertaining to NUPLAZID, we may need to resort to litigation to enforce other patents issued to us, protect our trade secrets or determine the scope and validity of third-party proprietary rights. From time to time, we may hire scientific personnel formerly employed by other companies involved in one or more areas similar to the activities conducted by us. Either we or these individuals may be subject to allegations of trade secret misappropriation or other similar claims as a result of their prior affiliations. If we become involved in litigation, it could consume a substantial portion of our managerial and financial resources, regardless of whether we win or lose. We may not be able to afford the costs of litigation. Any legal action against us or our collaborators could lead to:

- payment of damages, which could potentially be trebled if we are found to have willfully infringed a party's patent rights;
- injunctive or other equitable relief that may effectively block our ability to further develop, commercialize, and sell products; or
- we or our collaborators having to enter into license arrangements that may not be available on commercially acceptable terms, or at all.

As a result, we could be prevented from commercializing current or future products.

Furthermore, because of the substantial amount of pre-trial document and witness 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. In addition, during the course of this kind of litigation, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the trading price of our common stock.

The patent applications of pharmaceutical and biotechnology companies involve highly complex legal and factual questions, which, if determined adversely to us, could negatively impact our patent position.

The strength of patents in the pharmaceutical and biotechnology field can be highly uncertain and involve complex legal and factual questions. For example, some of our patent applications may cover the uses of gene sequences. The patentability of gene sequences and the use of gene sequences has been seriously undermined by recent decisions of the U.S. Supreme Court. The U.S. PTO's interpretation of the Supreme Court's decisions and the standards for patentability it sets forth are uncertain and could change in the future. Consequently, the issuance and scope of patents cannot be predicted with certainty. Patents, if issued, may be challenged, invalidated or circumvented. U.S. patents and patent applications may also be subject to interference proceedings as mentioned above, and U.S. patents may be subject to reexamination and post-issuance proceedings in the U.S. PTO (and foreign patents may be subject to opposition or comparable proceedings in the corresponding foreign patent office), which proceedings could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. Similarly, opposition or invalidity proceedings could result in loss of rights or reduction in the scope of one or more claims of a patent in foreign jurisdictions. In addition, such interference, reexamination, post-issuance and opposition proceedings may be costly. Accordingly, rights under any issued patents may not provide us with sufficient protection against competitive products or processes.

In addition, changes in or different interpretations of patent laws in the U.S. and foreign countries may permit others to use our discoveries or to develop and commercialize our technology and products without providing any compensation to us or may limit the number of patents or claims we can obtain. In particular, there have been proposals to shorten the exclusivity periods available under U.S. patent law that, if adopted, could substantially harm our business. The product candidates that we are developing are protected by intellectual property rights, including patents and patent applications. If any of our product candidates becomes a marketable product, we will rely on our exclusivity under patents to sell the compound and recoup our investments in the research and development of the compound. If the exclusivity period for patents is shortened, then our ability to generate revenues without competition will be reduced and our business could be materially adversely impacted. The laws of some countries do not protect intellectual property rights to the same extent as U.S. laws and those countries may lack adequate rules and procedures for defending our intellectual property rights. For example, some countries, including many in Europe, do not grant patent claims directed to methods of treating humans and, in these countries, patent protection may not be available at all to protect our product candidates. In addition, U.S. patent laws may change which could prevent or limit us from filing patent applications or patent claims to protect our products and/or technologies or limit the exclusivity periods that are available to patent holders. For example, the America Invents Act (2012) included a number of significant changes to U.S. patent law. These included changes to transition from a "first-to-invent" system to a "first-to-file" system and to the way issued patents are challenged. These changes may favor larger and more established companies that have more resources to devote to patent application filing and prosecution. It is still not clear what, if any, impact the America Invents Act will ultimately have on the cost of prosecuting our patent applications, our ability to obtain patents based on our discoveries and our ability to enforce or defend our issued patents.

If we fail to obtain and maintain patent protection and trade secret protection of our product candidates, proprietary technologies and their uses, we could lose our competitive advantage and competition we face would increase, reducing our potential revenues and adversely affecting our ability to attain or maintain profitability.

Risks Related to Government Regulation and Our Industry

Healthcare reform measures may negatively impact our ability to sell NUPLAZID or our product candidates, if approved, profitably.

In both the U.S. and certain foreign jurisdictions, there have been a number of legislative and regulatory proposals to change the healthcare system in ways that could impact our ability to sell NUPLAZID, and any other potential products, as described in greater detail in the Government Regulation section of our Annual Report.

For example, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively the ACA), 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 may receive for any approved product, including NUPLAZID. With respect to pharmaceutical products, the ACA, among other things, expanded and increased industry rebates for drugs covered by Medicaid and made changes to the coverage requirements under Medicare Part D, Medicare's prescription drug benefits program. There have been legal and political challenges to certain aspects of the ACA. For example, the 2017 Tax Act included a provision that repealed, effective January 1, 2019, 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 that is commonly referred to as the "individual mandate". In addition, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and the medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. The Bipartisan Budget Act of 2018 (BBA), among other things, amended the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole", and also increased the percentage that a drug manufacturer must discount the cost of prescription drugs from 50% to 70%. Given that the current patient population for NUPLAZID is primarily Medicare beneficiaries, accelerating the closure of the coverage gap and the increase in the discount that must be paid, could have a significant impact on the Company's business in 2021 and beyond. Furthermore, on June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the ACA will remain in effect in its current form. Moreover, prior to the U.S. Supreme Court ruling, on January 28, 2021, President Biden issued an executive order that initiated a special enrollment period for purposes of obtaining health insurance coverage through the ACA marketplace, which began on February 15, 2021 and remained open through August 15, 2021. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is unclear how any such challenges and other litigation, and the healthcare reform measures of the Biden administration will impact the ACA and our business.

Other legislative changes have been proposed and adopted in the U.S. since the ACA. Through the process created by the Budget Control Act of 2011, there are automatic reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments, including the Infrastructure Investment and Jobs Act, will remain in effect through 2031 unless additional Congressional action is taken. However, COVID-19 pandemic relief legislation suspended the 2% Medicare sequester from May 1, 2020 through March 31, 2022. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates 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. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to certain providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In addition, Congress is considering additional health reform measures as part of the budget reconciliation process.

An expansion in the government's role in the U.S. healthcare industry may increase existing congressional or governmental agency scrutiny on price increases, such as the ones we have implemented for NUPLAZID, cause general downward pressure on the prices of prescription drug products, lower reimbursements for providers using NUPLAZID or any other product for which we obtain regulatory approval, reduce product utilization and adversely affect our business and results of operations. There have been several recent U.S. presidential executive orders, Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform

government program reimbursement methodologies for drugs. For example, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that attempt to implement several of the administration's proposals. The FDA concurrently released a final rule and guidance in September 2020 implementing a portion of former President Trump's importation executive order announced in July 2020, providing pathways for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, the Department of Health and Human Services (HHS) finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of this rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a new safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed until January 1, 2023. In addition, on November 20, 2020, the Centers for Medicare and Medicaid Services (CMS) issued an interim final rule implementing former President Trump's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries, effective January 1, 2021. As a result of litigation challenging the Most Favored Nation model, on December 27, 2021, CMS published a final rule that rescinded the Most Favored Nation model interim final rule. Further, in July 2021, the Biden administration released an executive order that included multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform. The plan sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. Individual states in the U.S. have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

The implementation of cost-containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize NUPLAZID or any other products for which we may receive regulatory approval. It is also possible that additional governmental action may be taken in response to the COVID-19 pandemic.

We are subject, directly and indirectly, to federal, state and foreign healthcare and data protection laws and regulations, including healthcare fraud and abuse laws, false claims laws, physician payment transparency laws and health information privacy and security laws. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

Our operations are directly, and indirectly through our customers and third-party payors, subject to various U.S. federal and state healthcare laws and regulations, including, without limitation, the U.S. federal Anti-Kickback Statute, the U.S. federal False Claims Act, and physician payment sunshine laws and regulations. These laws may impact, among other things, our clinical research, sales, marketing, grants, charitable donations, and education programs and constrain the business or financial arrangements with healthcare providers, physicians, charitable foundations that support Parkinson's disease patients generally, and other parties that have the ability to directly or indirectly influence the prescribing, ordering, marketing, or distribution of our products for which we obtain marketing approval. In addition, we and any current or potential future collaborators, partners or service providers are or may become subject to data privacy and security regulation by both the U.S. federal government and the states in which we conduct our business, including laws and regulations that apply to our processing of personal data or the processing of personal data on our behalf. Finally, we may be subject to additional healthcare, statutory and regulatory requirements and enforcement by foreign regulatory authorities in jurisdictions in which we conduct our business. The laws that may affect our ability to operate include:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or paying any remuneration (including any kickback, bribe, or certain rebates), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service, for which payment may be made, in whole or in part, under U.S. federal and state healthcare programs such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the U.S. federal civil and criminal false claims laws, including the civil False Claims Act, which can be enforced through civil whistleblower or *qui tam* actions, and civil monetary penalties laws, which impose criminal and civil penalties on individuals or entities for, among other things, knowingly presenting, or causing to be presented to the U.S. federal government, claims for payment or approval that are false or fraudulent or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- the U.S. federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or 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, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, and its implementing regulations, and as amended again by the Final HIPAA Omnibus Rule, Modifications to the HIPAA Privacy, Security, Enforcement and Breach Notification Rules Under the Health Information Technology for Economic and Clinical Health Act (HITECH) and the Genetic Information Nondiscrimination Act; Other Modifications to the HIPAA Rules, published in January 2013, which imposes certain obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information on covered entities subject to the rule, such as health plans, healthcare clearinghouses and certain healthcare providers as well as their business associates, individuals or entities that perform certain services involving the use or disclosure of individually identifiable health information on behalf of a covered entity and their subcontractors that use, disclose or otherwise process individually identifiable health information;
- the U.S. Federal Food, Drug and Cosmetic Act (FDCA), which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;
- the U.S. federal physician payment transparency requirements, sometimes referred to as the “Physician Payments Sunshine Act”, which was enacted as part of the ACA and its implementing regulations and requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid, or the Children’s Health Insurance Program to report annually to CMS information related to certain payments and other transfers of value made to physicians (as defined to include doctors of medicine, dentists, optometrists, podiatrists and chiropractors under such law), other healthcare professionals (such as physician assistants and nurse practitioners), and teaching hospitals, as well as information regarding ownership and investment interests held by physicians and their immediate family members;
- analogous state and local laws and regulations, including: state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state and local laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities and/or the registration of pharmaceutical sales representatives; and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts; and

- European and other foreign law equivalents of each of the laws, including reporting requirements detailing interactions with and payments to healthcare providers and personal data protection, such as the European General Data Protection Regulation (EU) 2016/679 (GDPR), which became effective in May 2018 and contains new provisions specifically directed at the processing of health information, higher sanctions and extra-territoriality measures intended to bring non-EU companies under the regulation, including companies like us that conduct clinical trials in the European Economic Area (EEA); we anticipate that over time we may expand our business operations to include additional operations in the EU and with such expansion, we would be subject to increased governmental regulation in the EU countries in which we might operate, including the GDPR.

The GDPR has increased our responsibility and liability in relation to personal data that we process where such processing is subject to the GDPR, and we may be required to put in place additional mechanisms to ensure compliance with the GDPR, including as implemented by individual countries. Failure to comply with the GDPR carries significant risk as potential fines for noncompliant companies of are up to the greater of €20 million or 4% of annual global revenue and potential penalties include a prohibition on use of personal data subject to the GDPR, which could impact our operations and ability to develop our products and provide our services, including interrupting or ending EEA clinical trials. Compliance with the GDPR and the laws and regulations of applicable EU Member States and similar data protection laws in domestic and other foreign jurisdictions (such as Switzerland and the United Kingdom) is a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, and reputational harm in connection with our activities.

In addition, certain jurisdictions have enacted data localization laws and laws regulating or restricting cross-border personal data transfers. For example, European data protection laws, including the GDPR, generally restrict the transfer of personal data from Europe, including the EEA, United Kingdom and Switzerland, to the United States and most other countries unless the parties to the transfer have implemented specific safeguards to protect the transferred personal data. A decision by the Court of Justice of the European Union (the “Schrems II” ruling), however, invalidated the EU-U.S. Privacy Shield Framework, which was one of the primary mechanisms used by U.S. companies, including us, to import personal data from Europe, and raised questions about whether the European Commission’s Standard Contractual Clauses (SCCs), one of the primary alternatives to the Privacy Shield, can lawfully be used for personal information transfers from Europe to the U.S. or most other countries. Similarly, the Swiss Federal Data Protection and Information Commissioner opined that the Swiss-U.S. Privacy Shield is inadequate for transfers of personal data from Switzerland to the U.S. The United Kingdom, whose data protection laws are similar to those of the European Union, may similarly determine that the EU-U.S. Privacy Shield is not a valid mechanism for lawfully transferring personal information from the UK to the U.S. In June 2021, the European Commission released a set of “Standard Contractual Clauses” that are designed to be a valid mechanism by which entities can transfer personal data out of the EEA to jurisdictions that the European Commission has not found to provide an adequate level of protection. Currently, these Standard Contractual Clauses are a valid mechanism to transfer personal data outside of the EEA. The Standard Contractual Clauses, however, require parties that rely upon them to comply with additional obligations, such as conducting transfer impact assessments to determine whether additional security measures are necessary to protect the at-issue personal data. Moreover, due to potential legal challenges, there exists some uncertainty regarding whether the Standard Contractual Clauses will remain a valid mechanism for transfers of personal data out of the EEA. If we are unable to implement a valid compliance mechanism for cross-border personal data transfers, we may face increased exposure to regulatory actions, substantial fines and injunctions against processing or transferring personal data. For example, inability to import personal data from Europe to the United States may limit our ability to conduct clinical trial activities in Europe, limit our ability to collaborate with contract research organizations, service providers, contractors and other entities subject to European data protection laws, adversely impact our operations, product development and ability to provide our products, and require us to increase our data processing capabilities in Europe at significant expense.

Further, the United Kingdom’s vote in favor of exiting the EU, often referred to as Brexit, has created uncertainty with regard to data protection regulation in the United Kingdom. The data protections in the GDPR continue to apply to United Kingdom-related processing of personal data in substantially unvaried form under the so-called “UK GDPR.” However, going forward, there will be increasing potential for divergence in the application and interpretation of the data protection laws as between the United Kingdom and the EEA. Furthermore, the relationship between the United Kingdom and the EEA in relation to certain aspects of data protection law remains somewhat uncertain. On June 28, 2021, the European Commission issued an adequacy decision under the GDPR which allows personal data transfers from the EEA to the United Kingdom to continue without restriction for four years (ending June 27, 2025). After that period, the adequacy decision may be renewed, however, only if the United Kingdom continues to ensure an adequate level of data protection. During this time, the European Commission will continue to monitor the situation in the United Kingdom and could intervene at any point if the United Kingdom deviates from the level of data protection in place at the time of the issuance of the adequacy decision. If the adequacy decision is withdrawn or not renewed, transfers of personal data from the EEA to the United Kingdom will

require a valid ‘transfer mechanism’ and we may be required to implement new processes and put new agreements in place, such as SCCs, to enable transfers of personal data form the EEA to the United Kingdom to continue.

Moreover, states in the U.S. are constantly adopting new data protection laws or amending existing laws, requiring attention to frequently changing regulatory requirements. For example, the California Consumer Privacy Act of 2018 (CCPA), imposes obligations on businesses to which it applies. These obligations include, without limitation, providing specific disclosures in privacy notices, affording California residents certain rights to their personal data, and requiring businesses subject to the CCPA to implement certain measures to effectuate California residents’ personal data rights. The CCPA allows for statutory fines for noncompliance (up to $7,500 per violation). In addition, it is anticipated that the California Privacy Rights Act of 2020 (CPRA), effective January 1, 2023, will expand the CCPA. For example, the CPRA establishes a new California Privacy Protection Agency to enforce the CCPA (as amended), which could increase the risk of an enforcement action. Although the CCPA and the CPRA exempt some personal information processed in the context of clinical trials, these laws, to the extent applicable to our business and operations, may increase our potential liability with respect to other personal information we maintain about California residents. Moreover, other states have enacted data privacy laws. For example, Virginia passed the Consumer Data Protection Act and Colorado passed the Colorado Privacy Act, both of which differ from the CPRA and become effective in 2023.

Compliance with U.S. and foreign data protection laws and regulations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose personal data, or in some cases, impact our ability to operate in certain jurisdictions. Data protection laws worldwide are, and are likely to remain, uncertain for the foreseeable future. While we strive to comply with applicable data protection laws, external and internal privacy and security policies, and contractual data protection obligations and other data protection obligations to the extent possible, we may at times fail to do so, or may be perceived to have failed to do so. Moreover, despite our efforts, we may not be successful in achieving compliance if our personnel, collaborators, partners or vendors do not comply with applicable data protection obligations. Actual or perceived failure to comply with our protection obligations could result in government enforcement actions (which could include civil or criminal penalties), investigations, private litigation, other liabilities and/or adverse publicity and could negatively affect our operating results and business. Moreover, clinical trial subjects about whom we or our potential collaborators obtain information, as well as the providers who share this information with us, may contractually limit our ability to use and disclose the information. Claims that we have violated individual’s privacy rights, even if we are found not liable, could be expensive and time consuming to defend.

We are also subject to the terms of our external and internal privacy and security policies, representations, certifications, publications and frameworks, and contractual obligations to third parties related to privacy, information security and processing. Failure or a perceived failure to comply with these policies, or if these policies are, in whole or part, found or perceived to be inaccurate, incomplete, deceptive, unfair, or misrepresentative of our actual practices, could result in reputational harm; result in litigation; cause a material adverse impact to business operations or financial results, and; otherwise result in other material harm to our business.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations could involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. For example, contributions to third-party charitable foundations are a current area of significant governmental and congressional scrutiny, and we could face action if a federal or state governmental authority were to conclude that our charitable contributions to foundations that support Parkinson’s disease patients generally are not compliant. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from U.S. government-funded healthcare programs, such as Medicare and Medicaid, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits, additional reporting requirements and/or oversight, and the curtailment or restructuring of our operations. Moreover, while we do not bill third-party payors directly and our customers make the ultimate decision on how to submit claims, from time-to-time, for NUPLAZID, and any other product candidates that may be approved, we may provide reimbursement guidance to patients and healthcare providers. If a government authority were to conclude that we provided improper advice and/or encouraged the submission of a false claim for reimbursement, we could face action against us by government authorities. If any of the physicians or other providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government-funded healthcare programs and imprisonment. If any of the above occur, it could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of NUPLAZID, or any other product

candidates that may be approved, outside the U.S. will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the U.S., we could be subject to additional reimbursement requirements, fines, sanctions and exposure under other laws which could have a material adverse effect on our business, results of operations and financial condition.

We participate in the Medicaid Drug Rebate Program, as administered by CMS, and other federal and state government pricing programs in the U.S., and we may participate in additional government pricing programs in the future. These programs generally require us to pay rebates or otherwise provide discounts to government payors in connection with drugs that are dispensed to beneficiaries/recipients of these programs. In some cases, such as with the Medicaid Drug Rebate Program, the rebates are based on pricing that we report on a monthly and quarterly basis to the government agencies that administer the programs. Pricing requirements and rebate/discount calculations are complex, vary among products and programs, and are often subject to interpretation by governmental or regulatory agencies and the courts. The requirements of these programs, including, by way of example, their respective terms and scope, change frequently. For example, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price (AMP), for single source and innovator multiple source drugs, beginning January 1, 2024. Responding to current and future changes may increase our costs, and the complexity of compliance will be time consuming. Invoicing for rebates is provided in arrears, and there is frequently a time lag of up to several months between the sales to which rebate notices relate and our receipt of those notices, which further complicates our ability to accurately estimate and accrue for rebates related to the Medicaid program as implemented by individual states. Thus, there can be no assurance that we will be able to identify all factors that may cause our discount and rebate payment obligations to vary from period to period, and our actual results may differ significantly from our estimated allowances for discounts and rebates. Changes in estimates and assumptions may have a material adverse effect on our business, results of operations and financial condition.

In addition, the HHS Office of Inspector General and other Congressional, enforcement and administrative bodies have recently increased their focus on pricing requirements for products, including, but not limited to the methodologies used by manufacturers to calculate AMP, and best price (BP), for compliance with reporting requirements under the Medicaid Drug Rebate Program. We are liable for errors associated with our submission of pricing data and for any overcharging of government payors. For example, failure to submit monthly/quarterly AMP and BP data on a timely basis could result in significant civil monetary penalties for each day the submission is late beyond the due date. Failure to make necessary disclosures and/or to identify overpayments could result in allegations against us under the civil False Claims Act and other laws and regulations. Any required refunds to the U.S. government or responding to a government investigation or enforcement action would be expensive and time consuming and could have a material adverse effect on our business, results of operations and financial condition. In addition, in the event that the CMS were to terminate our rebate agreement, no federal payments would be available under Medicaid or Medicare for our covered outpatient drugs.

The FDA granted marketing approval of NUPLAZID for the treatment of hallucinations and delusions associated with PDP, and we could face liability if a regulatory authority determines that we are promoting NUPLAZID for any "off-label" uses.

A company may not promote "off-label" uses for its drug products. An off-label use is the use of a product for an indication or patient population that is not described in the product's FDA-approved label in the U.S. or for uses in other jurisdictions that differ from those approved by the applicable regulatory agencies. Physicians, on the other hand, may prescribe products for off-label uses. Although the FDA and other regulatory agencies do not regulate a physician's choice of drug treatment made in the physician's independent medical judgment, they do restrict promotional communications from pharmaceutical companies or their sales force with respect to off-label uses of products for which marketing clearance has not been issued. A company that is found to have promoted off-label use of its product may be subject to significant liability, including civil and criminal sanctions. We intend to comply with the requirements and restrictions of the FDA and other regulatory agencies with respect to our promotion of NUPLAZID, and any other products we may market, but we cannot be sure that the FDA or other regulatory agencies will agree that we have not violated their restrictions. As a result, we may be subject to criminal and civil liability. In addition, our management's attention could be diverted to handle any such alleged violations. A significant number of pharmaceutical companies have been the target of inquiries and investigations by various U.S. federal and state regulatory, investigative, prosecutorial and administrative entities in connection with the promotion of products for unapproved uses and other sales practices, including the Department of Justice (DOJ), and various U.S. Attorneys' Offices, the HHS Office of Inspector General, the FDA, the Federal Trade Commission and various state

Attorneys General offices. These investigations have alleged violations of various U.S. federal and state laws and regulations, including claims asserting antitrust violations, violations of the FDCA, the civil False Claims Act, the Prescription Drug Marketing Act, anti-kickback laws, and other alleged violations in connection with the promotion of products for unapproved uses, pricing and Medicare and/or Medicaid reimbursement. If the FDA, DOJ, or any other governmental agency initiates an enforcement action against us, or if we are the subject of a qui tam suit and it is determined that we violated prohibitions relating to the promotion of products for unapproved uses, we could be subject to substantial civil or criminal fines or damage awards and other sanctions such as consent decrees and corporate integrity agreements pursuant to which our activities would be subject to ongoing scrutiny and monitoring to ensure compliance with applicable laws and regulations. Any such fines, awards or other sanctions would have an adverse effect on our revenue, business, financial prospects, and reputation.

Changes at the FDA and other government agencies could delay or prevent new products from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including beginning on December 22, 2018 and ending on January 25, 2019, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical government employees and stop critical activities. If repeated or prolonged government shutdowns occur, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, and negatively impact other government operations on which we rely, which could have a material adverse effect on our business. In addition, the COVID-19 pandemic may affect processing times as the FDA reallocates resources to immediate needs such as the review and approval of viral and antibody tests, therapeutic treatments for use by COVID-19 patients and SARS-CoV-2 vaccines.

We are subject to stringent regulation in connection with the marketing of NUPLAZID and any other products derived from our product candidates, which could delay the development and commercialization of our products.

The pharmaceutical industry is subject to stringent regulation by the FDA and other regulatory agencies in the U.S. and by comparable authorities in other countries. Neither we nor our collaborators can market a pharmaceutical product, including NUPLAZID, in the U.S. until it has completed rigorous preclinical testing and clinical trials and an extensive regulatory clearance process implemented by the FDA. Satisfaction of regulatory requirements typically takes many years, depends upon the type, complexity and novelty of the product, and requires substantial resources. Even if regulatory approval is obtained, the FDA and other regulatory agencies may impose significant restrictions on the indicated uses, conditions for use, labeling, advertising, promotion, and/or marketing of such products, and requirements for post-approval studies, including additional research and development and clinical trials. These limitations may limit the size of the market for the product or result in the incurrence of additional costs. Any delay or failure in obtaining required approvals could have a material adverse effect on our ability to generate revenues from the particular product candidate.

Outside the U.S., the ability to market a product is contingent upon receiving approval from the appropriate regulatory authorities. The requirements governing the conduct of clinical trials, marketing authorization, pricing, and reimbursement vary widely from country to country. Only after the appropriate regulatory authority is satisfied that adequate evidence of safety, quality, and efficacy has been presented will it grant a marketing authorization. Approval by the FDA does not automatically lead to the approval by regulatory authorities outside the U.S. and, similarly, approval by regulatory authorities outside the U.S. will not automatically lead to FDA approval.

In addition, U.S. and foreign government regulations control access to and use of some human or other tissue samples in our research and development efforts. U.S. and foreign government agencies may also impose restrictions on the use of data derived from human or other tissue samples. Accordingly, if we fail to comply with these regulations and restrictions, the commercialization of our product candidates may be delayed or suspended, which may delay or impede our ability to generate product revenues.

If our competitors develop and market products that are more effective than NUPLAZID or our product candidates, they may reduce or eliminate our commercial opportunity.

Competition in the pharmaceutical and biotechnology industries is intense and expected to increase. We face competition from pharmaceutical and biotechnology companies, as well as numerous academic and research institutions and governmental agencies, both in the U.S. and abroad. Some of these competitors have products or are pursuing the development of drugs that target the same diseases and conditions that are the focus of our drug development programs.

For example, the use of NUPLAZID for the treatment of PDP competes with off-label use of various antipsychotic drugs, including the generic drugs quetiapine, clozapine, risperidone, aripiprazole, and olanzapine. If approved, pimavanserin for the treatment of ADP would also compete with off-label use of various antipsychotic drugs, including the generic drugs quetiapine, clozapine, risperidone, aripiprazole, and olanzapine, as well as generic mood stabilizers such as valproate. Other generic agents for the treatment of underlying dementia such as donepezil and memantine may also be secondarily used for the treatment of ADP, although NUPLAZID would not be promoted to replace these agents. Pimavanserin for the treatment of negative symptoms of schizophrenia, if approved for that indication, would compete with off-label use of Vraylar, marketed by Allergan, Rexulti, marketed by Otsuka Pharmaceutical Co., Ltd., Latuda, marketed by Sunovion Pharmaceuticals Inc., Caplyta, marketed by IntraCellular Therapeutics and various generic drugs, including quetiapine, clozapine, risperidone, aripiprazole, and olanzapine. In addition, trofinetide, if approved would compete indirectly with off-label usage of branded and generic prescription medications targeted at individual symptoms of Rett syndrome, including antiepileptics, antipsychotics, antidepressants and benzodiazepines. Several academic institutions and pharmaceutical companies are currently conducting clinical trials for the treatment of various symptoms of Rett syndrome.

Many of our competitors and their collaborators have significantly greater experience than we do in the following:

- identifying and validating targets;
- screening compounds against targets;
- preclinical studies and clinical trials of potential pharmaceutical products;
- obtaining FDA and other regulatory approvals; and
- commercializing pharmaceutical products.

In addition, many of our competitors and their collaborators have substantially greater capital and research and development resources, manufacturing, sales and marketing capabilities, and production facilities. Smaller companies also may prove to be significant competitors, particularly through proprietary research discoveries and collaboration arrangements with large pharmaceutical and established biotechnology companies. Many of our competitors have products that have been approved or are in advanced development and may develop superior technologies or methods to identify and validate drug targets and to discover novel small molecule drugs. Our competitors, either alone or with their collaborators, may succeed in developing drugs that are more effective, safer, more affordable, or more easily administered than ours and may achieve patent protection or commercialize drugs sooner than us. Our competitors may also develop alternative therapies that could further limit the market for any drugs that we may develop. Our failure to compete effectively could have a material adverse effect on our business.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of NUPLAZID or any other product for which we obtain regulatory approval, or development or commercialization of our product candidates.

We face an inherent risk of product liability as a result of the commercial sales of NUPLAZID in the U.S. and the clinical testing of our product candidates, and will face an even greater risk following commercial launch of NUPLAZID in additional jurisdictions, if approved, or if we engage in the clinical testing of new product candidates or commercialize any additional products. For example, we may be sued if NUPLAZID or any other product we develop allegedly causes injury or is found to be otherwise unsuitable for administration in humans. 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. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our products or product candidates that we may develop;

- injury to our reputation;
- withdrawal of clinical trial participants;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize our products or product candidates; and
- a decline in our stock price.

Although we currently have product liability insurance that covers our clinical trials and the commercialization of NUPLAZID, we may need to increase and expand this coverage, including if we commence larger scale trials and if other product candidates are approved for commercial sale. This insurance may be prohibitively expensive or may not fully cover our potential liabilities. Inability to obtain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims could prevent or inhibit the commercialization of products that we or our collaborators develop. If we determine that it is prudent to increase our product liability coverage, we may be unable to obtain such increased coverage on acceptable terms or at all. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. Our liability could exceed our total assets if we do not prevail in a lawsuit from any injury caused by our drug products. Product liability claims could have a material adverse effect on our business and results of operations.

If our information technology systems or data is compromised, we could experience adverse impacts, including but not limited to interruptions to operations or clinical trials, claims that we failed to comply with our data protection obligations, harm to our reputation, and a loss of customers or sales.

In the ordinary course of our business, we may collect, store, use, transmit, disclose or otherwise process proprietary, confidential, and sensitive data, including personal data (such as health-related data), intellectual property, and trade secrets. We may rely upon third-parties (such as service providers) for our data processing-related activities. We may share or receive sensitive data with or from third parties.

Cyberattacks, malicious internet-based activity, and online and offline fraud are prevalent and continue to increase. These threats are becoming increasingly difficult to detect. These threats come from a variety of sources, including traditional computer "hackers," threat actors, personnel misconduct or error (such as through theft or misuse), sophisticated nation-states, and nation-state-supported actors. We and the third parties upon which we rely may be subject to a variety of evolving threats, including but not limited to, social engineering attacks (including through phishing attacks), malicious code (such as viruses and worms), malware (including as a result of advanced persistent threat intrusions), denial-of-service attacks (such as credential stuffing), ransomware attacks, supply-chain attacks, software bugs, server malfunction, software or hardware failures, loss of data or other information technology assets, adware, telecommunications failures, earthquakes, fire, flood, and other similar threats.

Ransomware attacks, including by organized criminal threat actors, nation-states, and nation-state-supported actors, are becoming increasingly prevalent and severe and can lead to significant interruptions, delays, or outages in our operations, disruption of clinical trials, loss of data (including data related to clinical trials), loss of data and income, significant extra expenses to restore data or systems, reputational harm and the diversion of funds. Extortion payments may alleviate the negative impact of a ransomware attack, but we may be unwilling or unable to make such payments (including, for example, if applicable laws or regulations prohibit such payments). Similarly, supply chain attacks have increased in frequency and severity, and we cannot guarantee that third parties and infrastructure in our supply chain have not been compromised or that they do not contain exploitable defects or bugs that could result in a breach of or disruption to our information technology systems and networks or the those of third parties that support us.

Despite the security controls we have in place, such attacks are difficult to avoid. Moreover, the prevalent use of mobile devices that access confidential information increases the risk of data security breaches, which could lead to the loss of confidential information, trade secrets or other intellectual property. For example, due to the COVID-19 pandemic and the potential that our personnel may work remotely, there may exist an increased risk to our information technology assets and data. .

We may be required to expend significant resources, fundamentally change our business activities and practices (including our clinical trials) or modify our operations or information technology in an effort to protect against security breaches and to mitigate, detect, and remediate actual and potential vulnerabilities, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us. A security breach or privacy violation that leads to disclosure or modification of or prevents access to patient/ trial participant information, including personally identifiable information or protected health information, or a perceived security breach or violation, could harm our reputation, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, subject us to investigations by federal or state authorities, require us to verify the correctness of database contents, and otherwise subject us to litigation or other liability under our data protection obligations, any of which could disrupt our business and/or result in increased costs or loss of revenue. Additionally, violations of our external contractual commitments and internal privacy and security policies may require us to notify relevant stakeholders if there has been a security breach, including affected individuals, business partners and regulators. Such disclosures are costly, and the disclosures or the failure to comply with such requirements could lead to a materially adverse impact on the business, including negative publicity, a loss of confidence in our services or security measures by our business partners or breach of contract claims.

Further, a security breach could result in temporary or permanent bans on all or some processing of personal data, which could impact our clinical trials or other development of our products. Moreover, security breaches can result in the diversion of funds, and interruptions, delays or outages in our operations. Failures or significant downtimes of or information technology or telecommunication systems or those used by the third parties upon whom we rely could cause significant interruptions in our operations and could adversely impact the confidentiality, integrity, and availability of sensitive information, including preventing us from conducting clinical trials, tests or research and development activities and preventing us from managing the administrative aspects of our business.

There can be no assurances that the limitations of liability in our contracts would be enforceable or adequate or would otherwise protect us from liabilities or damages if we fail to comply with applicable data protection laws, privacy policies or other data protection obligations related to information security or security breaches. While we have invested, and continue to invest, in the protection of our data and information technology infrastructure, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm to us.

In addition, our insurance coverage may not be sufficient in type or amount to cover us against claims related to privacy and security practices. The successful assertion of one or more large claims against us that exceeds our available insurance coverage, or results in changes to our insurance policies (including premium increases or the imposition of large deductible or co-insurance requirements), could have an adverse effect on our business.

Risks Related to Our Common Stock

Our stock price historically has been, and is likely to remain, highly volatile.

The market prices for securities of biotechnology companies in general, and drug discovery and development companies in particular, have been highly volatile and may continue to be highly volatile in the future. The following factors, in addition to other risk factors described in this section, may have a significant impact on the market price of our common stock:

- the success of our commercialization of NUPLAZID in the U.S. for the treatment of hallucinations and delusions associated with PDP;
- the status and cost of our post-marketing commitments for NUPLAZID;
- the status and cost of development and commercialization of pimavanserin for indications other than in PDP, including ADP, and in jurisdictions other than the U.S.;

- the status and cost of development and commercialization of our product candidates, including compounds being developed under our collaborations;
- whether we acquire or in-license additional product candidates or products, and the status of development and commercialization of such product candidates or products;
- any other communications or guidance from the FDA or other regulatory authorities that pertain to NUPLAZID or our product candidates;
- the initiation, termination, or reduction in the scope of our collaborations or any disputes or developments regarding our collaborations;
- market conditions or trends related to biotechnology and pharmaceutical industries, or the market in general;
- announcements of technological innovations, new products, or other material events by our competitors or us, including any new products that we may acquire or in-license;
- disputes or other developments concerning our proprietary and intellectual property rights;
- changes in, or failure to meet, securities analysts' or investors' expectations of our financial performance;
- our failure to meet applicable Nasdaq listing standards and the possible delisting of our common stock from the Nasdaq Stock Market;
- additions or departures of key personnel;
- discussions of our business, products, financial performance, prospects, or stock price by the financial and scientific press and online investor communities such as blogs and chat rooms;
- public concern as to, and legislative action with respect to, genetic testing or other research areas of biopharmaceutical companies, the pricing and availability of prescription drugs, or the safety of drugs and drug delivery techniques;
- regulatory developments in the U.S. and in foreign countries;
- changes in the structure of healthcare payment systems;
- the announcement of, or developments in, any litigation matters;
- disruptions caused by man-made or natural disasters or public health pandemics or epidemics or other business interruptions, including, for example, the COVID-19 pandemic; and
- economic and political factors, including but not limited to economic and financial crises, wars, terrorism, and political unrest.

In the past, following periods of volatility in the market price of a particular company's securities, securities class action litigation has often been brought against that company. For example, we, and certain of our current and former officers and directors, are subject to numerous lawsuits related to prior statements about NUPLAZID and our sNDA seeking approval of pimavanserin for the treatment of hallucinations and delusions associated with DRP, as described in "Legal Proceedings". If we are not successful in defense of these claims, we may have to make significant payments to, or other settlements with, our stockholders and their attorneys. Even if such claims are not successful, the litigation could result in substantial costs and divert our management's attention and resources, which could have a material adverse effect on our business, operating results or financial condition.

If we or our stockholders sell substantial amounts of our common stock, the market price of our common stock may decline.

A significant number of shares of our common stock are held by a small number of stockholders. Sales of a significant number of shares of our common stock, or the expectation that such sales may occur, could significantly reduce the market price of our common stock. In connection with our March 2014 public offering of common stock, we agreed to provide resale registration rights for the shares of our common stock held by entities affiliated with one of our principal stockholders and two of our directors, Julian C. Baker and Dr. Stephen R. Biggar, which we refer to as the Baker Entities. In connection with our January 2016 public offering of common stock, we entered into a formal registration rights agreement with the Baker Entities to provide for these rights. Under the registration rights agreement we have agreed that, if at any time and from time to time, the Baker Entities demand that we register their shares of our common stock for resale under the Securities Act, we

would be obligated to effect such registration. On May 3, 2019, we filed a registration statement covering the sale of up to 40,203,111 shares of our common stock, which includes 489,269 shares of our common stock issuable upon the exercise of warrants that were owned by the Baker Entities as of April 29, 2019, and which represented approximately 28 percent of our outstanding shares at the time. Our registration obligations under this registration rights agreement cover all shares now held or later acquired by the Baker Entities will be in effect for up to 10 years, and include our obligation to facilitate certain underwritten public offerings of our common stock by the Baker Entities in the future. If the Baker Entities sell a large number of our shares, or the market perceives that the Baker Entities intend to sell a large number of our shares, this could adversely affect the market price of our common stock. We also may elect to sell an indeterminate number of shares on our own behalf pursuant to a registration statement or in a private placement, from time to time. Our stock price may decline as a result of the sale of the shares of our common stock included in any of these registration statements or future financings.

If our officers, directors, and largest stockholders choose to act together, they may be able to significantly influence our management and operations, acting in their best interests and not necessarily those of our other stockholders.

Our directors, executive officers and holders of 5% or more of our outstanding common stock and their affiliates beneficially own a substantial portion of our outstanding common stock. As a result, these stockholders, acting together, have the ability to significantly influence all matters requiring approval by our stockholders, including the election of all of our board members, amendments to our certificate of incorporation, going-private transactions, and the approval of mergers or other business combination transactions. The interests of this group of stockholders may not always coincide with our interests or the interests of other stockholders and they may act in a manner that advances their best interests and not necessarily those of our other stockholders.

Anti-takeover provisions in our charter documents and under Delaware law may make an acquisition of us more complicated and may make the removal and replacement of our directors and management more difficult.

Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that may delay or prevent a change in control, discourage bids at a premium over the market price of our common stock and adversely affect the market price of our common stock and the voting and other rights of the holders of our common stock. These provisions may also make it difficult for stockholders to remove and replace our board of directors and management. These provisions:

- establish that members of the board of directors may be removed only for cause upon the affirmative vote of stockholders owning at least a majority of our capital stock;
- authorize the issuance of “blank check” preferred stock that could be issued by our board of directors to increase the number of outstanding shares and prevent or delay a takeover attempt;
- limit who may call a special meeting of stockholders;
- establish advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings;
- prohibit our stockholders from making certain changes to our amended and restated certificate of incorporation or amended and restated bylaws except with $66^{2/3}$% stockholder approval; and
- provide for a board of directors with staggered terms.

We are also subject to provisions of the Delaware corporation law that, in general, prohibit any business combination with a beneficial owner of 15% or more of our common stock for three years unless the holder’s acquisition of our stock was approved in advance by our board of directors. Although we believe these provisions collectively provide for an opportunity to receive higher bids by requiring potential acquirors to negotiate with our board of directors, they would apply even if the offer may be considered beneficial by some stockholders.

We do not intend to pay dividends on our common stock in the foreseeable future; as such, you must rely on stock appreciation for any return on your investment.

To date, we have not paid any cash dividends on our common stock, and we do not intend to pay any dividends in the foreseeable future. Instead, we intend to retain any future earnings to fund the development and growth of our business. For this reason, the success of an investment in our common stock, if any, will depend on the appreciation of our common stock, which may not occur. There is no guarantee that our common stock will appreciate, and therefore, a holder of our common stock may not realize a return on his or her investment.

General Risk Factors

Our management has broad discretion over the use of our cash and we may not use our cash effectively, which could adversely affect our results of operations.

Our management has significant flexibility in applying our cash resources and could use these resources for corporate purposes that do not increase our market value, or in ways with which our stockholders may not agree. We may use our cash resources for corporate purposes that do not yield a significant return or any return at all for our stockholders, which may cause our stock price to decline.

We have incurred, and expect to continue to incur, significant costs as a result of laws and regulations relating to corporate governance and other matters.

Laws and regulations affecting public companies, including provisions of the Dodd-Frank Wall Street Reform and Consumer Protection Act that was enacted in July 2010, the provisions of the Sarbanes-Oxley Act of 2002 (SOX), and rules adopted or proposed by the SEC and by The Nasdaq Stock Market, have resulted in, and will continue to result in, significant costs to us as we evaluate the implications of these rules and respond to their requirements. In the future, if we are not able to issue an evaluation of our internal control over financial reporting, as required, or we or our independent registered public accounting firm determine that our internal control over financial reporting is not effective, this shortcoming could have an adverse effect on our business and financial results and the price of our common stock could be negatively affected. New rules could make it more difficult or more costly for us to obtain certain types of insurance, including director and officer liability insurance, and we may be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the coverage that is the same or similar to our current coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors and board committees, and as our executive officers. We cannot predict or estimate the total amount of the costs we may incur or the timing of such costs to comply with these rules and regulations.

Changes or modifications in financial accounting standards, including those related to revenue recognition, may harm our results of operations.

From time to time, the Financial Accounting Standards Board (FASB), either alone or jointly with other organizations, promulgates new accounting principles that could have an adverse impact on our financial position, results of operations or reported cash flows. In February 2016, the FASB issued Accounting Standards Update (ASU) No. 2016-02, *Leases (Topic 842)*, which requires a lessee to recognize a lease liability and a right-of-use asset for all leases with lease terms of more than 12 months. We adopted this new standard for the year beginning January 1, 2019. Consequently, all of our operating lease commitments were recognized as lease liabilities, with corresponding right-of-use assets, based on the present value of the remaining minimum rental payments under current leasing standards for existing operating leases. Upon adoption of the standard, we recorded a right-of-use asset and lease liability of approximately $12.0 million in our condensed consolidated balance sheets. We have elected the standard's package of practical expedients on adoption requiring no reassessment of whether any expired or existing agreements contain a lease, the classification of any expired or existing lease agreements, or initial direct costs for any existing leases. The majority of our leases are facility and equipment leases and are classified as operating leases under current lease guidance. Any difficulties in adopting or implementing any other new accounting standard, and to update or modify our internal controls as needed on a timely basis, could result in our failure to meet our financial reporting obligations, which could result in regulatory discipline and harm investors' confidence in us. Finally, if we were to change our critical accounting estimates, including those related to the recognition of product revenue, our operating results could be significantly affected.

Adverse securities and credit market conditions may significantly affect our ability to raise capital.

Historically, turmoil and volatility in the financial markets (including recent volatility as a result of the COVID-19 pandemic) have adversely affected the market capitalizations of many biotechnology companies, and generally made equity and debt financing more difficult to obtain. These events, coupled with other factors, may limit our access to financing in the future. This could have a material adverse effect on our ability to access funding on acceptable terms, or at all, and our stock price may suffer further as a result.

Item 1B. ***Unresolved Staff Comments.***

This item is not applicable.

Item 2. ***Properties.***

As of December 31, 2021, our primary facility consists of approximately 98,000 square feet of office space in San Diego, California. We also lease a facility in Princeton, New Jersey that covers approximately 25,000 square feet of office space, which is leased through January 2025.

Item 3. ***Legal Proceedings.***

Between July 19 and August 3, 2018, following negative publicity about NUPLAZID, three purported stockholders of ours filed putative securities class action complaints (captioned Staublein v. Acadia Pharmaceuticals, Inc., Case No. 18-cv-01647, Stone v. Acadia Pharmaceuticals Inc., Case No. 18-cv-01672, and Barglow v. Acadia Pharmaceuticals Inc., Case No. 18-cv-01812) in the U.S. District Court for the Southern District of California against us and certain of our current and former executive officers. Thereafter, several putative lead plaintiffs filed motions to consolidate the cases and to appoint a lead plaintiff. On January 3, 2019, the Court consolidated the cases under the caption In re Acadia Pharmaceuticals Inc. Securities Litigation, Case No. 18-cv-01647, and took the lead plaintiff motions under submission. On February 26, 2019, the Court appointed a lead plaintiff and lead counsel. Lead plaintiff filed a consolidated complaint on April 15, 2019. The consolidated complaint generally alleges that defendants violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 by making materially false and misleading statements regarding our business, operations, and prospects by failing to disclose that adverse events and safety concerns regarding NUPLAZID threatened initial and continuing FDA approval, and by failing to disclose that we engaged in business practices likely to attract regulatory scrutiny. The consolidated complaint seeks unspecified monetary damages and other relief. Defendants filed a motion to dismiss the consolidated complaint on June 7, 2019. On June 1, 2020, the Court granted the motion in part and gave lead plaintiff leave to file an amended complaint. On July 16, 2020, lead plaintiff filed the amended complaint. Defendants filed a motion to dismiss the amended complaint on August 28, 2020. Lead plaintiff opposed the motion on September 15, 2020. Defendants' reply in support of the motion to dismiss was filed on November 11, 2020. On March 29, 2021, the Court granted the defendants' motion to dismiss with leave to amend. On April 16, 2021, lead plaintiff filed a third amended complaint. Defendants filed a motion to dismiss the third amended complaint on May 31, 2021. The lead plaintiff opposed the motion on July 12, 2021 and Defendants filed their reply in support of their motion on August 11, 2021. On January 3, 2022, the Court issued an order and judgment dismissing lead plaintiff's third amended complaint without leave to amend and closing the case. The deadline to appeal the order and judgment expired on February 2, 2022.

On February 7, 2020, a purported stockholder of ours filed a derivative complaint (captioned Barney v. Davis et al., Case No. 20-cv-0238) in the U.S. District Court for the Southern District of California against our directors and certain of our current and former executive officers. The complaint asserts claims for breach of fiduciary duty, waste of corporate assets, and unjust enrichment arising from allegations similar to those in the federal securities class action described above. On September 9, 2020, the Court substituted plaintiffs and re-captioned the case Shumacher v. Davis et al., Case No. 20-cv-0238. On June 23, 2020, a second derivative complaint (captioned Lazarus v. Davis et al., Case No. 20-cv-0843) was filed in the U.S. District Court for the District of Delaware. On September 9, 2020, the Court transferred the Lazarus case to the U.S. District Court for the Southern District of California and re-captioned the case Lazarus v. Davis et al., Case No. 20-cv-1774. On January 15, 2021, the Court consolidated the cases under the name In re ACADIA Pharmaceuticals Inc. Stockholder Derivative Litigation, Case No. 20-cv-0238, appointed lead counsel for the plaintiffs, and designated the complaint in the Shumacher case as the operative complaint. The consolidated case is stayed until the defendants in the federal securities class action answer, or the federal securities class action is dismissed with prejudice and all appeals are exhausted, or any party to the stipulation to stay gives 15 days' written notice that it no longer consents to the voluntary stay. As discussed above, the federal securities class action was dismissed with prejudice on January 3, 2022, and the deadline to appeal that dismissal expired on February 2, 2022

On July 24, 2020, we filed complaints against (i) Aurobindo Pharma Limited and its affiliate Aurobindo Pharma USA, Inc. and (ii) Teva Pharmaceuticals USA, Inc. and its affiliate Teva Pharmaceutical Industries Ltd., and on July 30, 2020, we filed complaints against (i) Hetero Labs Limited and its affiliates Hetero Labs Limited Unit-V and Hetero USA Inc., (ii) MSN Laboratories Private Ltd. and its affiliate MSN Pharmaceuticals, Inc., and (iii) Zydus Pharmaceuticals (USA) Inc. and its affiliate Cadila Healthcare Limited. These complaints, which were filed in the United States District Court for the District of Delaware, allege infringement of certain of our Orange Book-listed patents covering NUPLAZID. The cases have been assigned to the Honorable Richard G. Andrews. On September 1, 2020, Aurobindo filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity. On September 22, 2020, we filed our answer to Aurobindo's counterclaims. On August 31, 2020, Teva filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity. On September 21, 2020, we filed our answer to Teva's counterclaims. On October 5, 2020, Hetero filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity. On October 26,

2020, we filed our answer to Hetero's counterclaims. On September 30, 2020, MSN filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity regarding certain of our Orange Book-listed patents covering NUPLAZID. On November 5, 2020, we filed our first amended complaint against MSN in the United States District Court for the District of Delaware, alleging infringement of certain of our Orange Book-listed patents covering NUPLAZID. On November 19, 2020, MSN filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity regarding certain of our Orange Book-listed patents covering NUPLAZID. On December 10, 2020, we filed our answer to MSN's counterclaims. On November 2, 2020, Zydus filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity. On November 23, 2020, we filed our answer to Zydus's counterclaims. On December 8, 2020, the parties' joint proposed scheduling order was entered by Judge Andrews. On April 7, 2021, we filed our first amended complaints against Hetero and Teva and our second amended complaint against MSN, to include an additional Orange Book-listed patent covering NUPLAZID. On April 8, 2021, we filed our first amended complaint against Zydus and on April 9, 2021, we filed our first amended complaint against Aurobindo. On April 20, 2021, MSN filed its answer, affirmative defenses, and counterclaims to our second amended complaint, seeking declaratory judgments of noninfringement and invalidity regarding certain of the our Orange Book-listed patents covering NUPLAZID. On April 21, 2021, Teva filed its answer, affirmative defenses, and counterclaims to our first amended complaint, seeking declaratory judgments of noninfringement and invalidity. On April 22, 2021, Zydus filed its answer, affirmative defenses, and counterclaims to our first amended complaint, seeking declaratory judgments of noninfringement and invalidity.

On April 22, 2021, Aurobindo filed its answer, affirmative defenses, and counterclaims to our first amended complaint, seeking declaratory judgments of noninfringement and invalidity. On May 11, 2021, we filed our answer to MSN's counterclaims. On May 12, we filed our answer to Teva's counterclaims. On May 13, we filed our answer to Zydus's counterclaims and our answer to Aurobindo's counterclaims. A joint trial in the matters is scheduled for May 15, 2023. We entered into an agreement effective April 22, 2021 with Hetero settling all claims and counterclaims in the litigation. The agreement allows Hetero to launch its generic pimavanserin product on July 27, 2038, subject to certain triggers for earlier launch. The Hetero case was dismissed by joint agreement on May 3, 2021.

On August 27, 2021, we filed our second amended complaint against Zydus to include an additional Orange Book-listed patent covering NUPLAZID. On September 10, 2021, Zydus filed its answer, affirmative defenses, and counterclaims to our second amended complaint, seeking declaratory judgments of noninfringement and invalidity. Also on September 10, 2021, the parties filed their Joint Claim Construction Chart. On October 1, 2021, we filed our answer to Zydus's counterclaims. On November 30, 2021, we filed a stipulation and proposed order to dismiss two of our Orange Book-listed patents covering NUPLAZID against Teva, which was ordered by the Court on December 1, 2021. On January 28, 2022, the parties filed their Joint Claim Construction Brief and Appendix. On January 31, 2022, a joint motion for claim construction was ordered by the Court, setting a claim construction hearing on February 23, 2022. A ruling is expected in the near future.

On April 19, 2021, a purported stockholder of ours filed a putative securities class action complaint (captioned Marechal v. Acadia Pharmaceuticals, Inc., Case No. 21-cv-0762) in the U.S. District Court for the Southern District of California against us and certain of our current executive officers. The complaint generally alleges that defendants violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 by making materially false and misleading statements regarding our business, operations, and prospects by failing to disclose that the materials submitted in support of our sNDA seeking approval of pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis contained statistical and design deficiencies and that the FDA was unlikely to approve the sNDA in its current form. The complaint seeks unspecified monetary damages and other relief. On June 21, 2021, five motions for lead plaintiff and lead counsel were filed. Thereafter, four of the five movants either withdrew their motions or filed statements of non-opposition. On September 29, 2021, the Court issued an order designating lead plaintiff and lead counsel. On December 10, 2021, lead plaintiff filed an amended complaint. Defendants filed a motion to dismiss the amended complaint on February 15, 2022.

We currently believe that none of the foregoing claims or actions pending against us as of December 31, 2021 is likely to have, individually or in the aggregate, a material adverse effect on our business, liquidity, financial position, or results of operations. Given the unpredictability inherent in litigation, however, we cannot predict the outcome of these matters. We are unable to estimate possible losses or ranges of losses that may result from these matters, and therefore we have not accrued any amounts in connection with these matters other than attorneys' fees incurred to date.

Item 4. ***Mine Safety Disclosures.***

This item is not applicable.

PART II

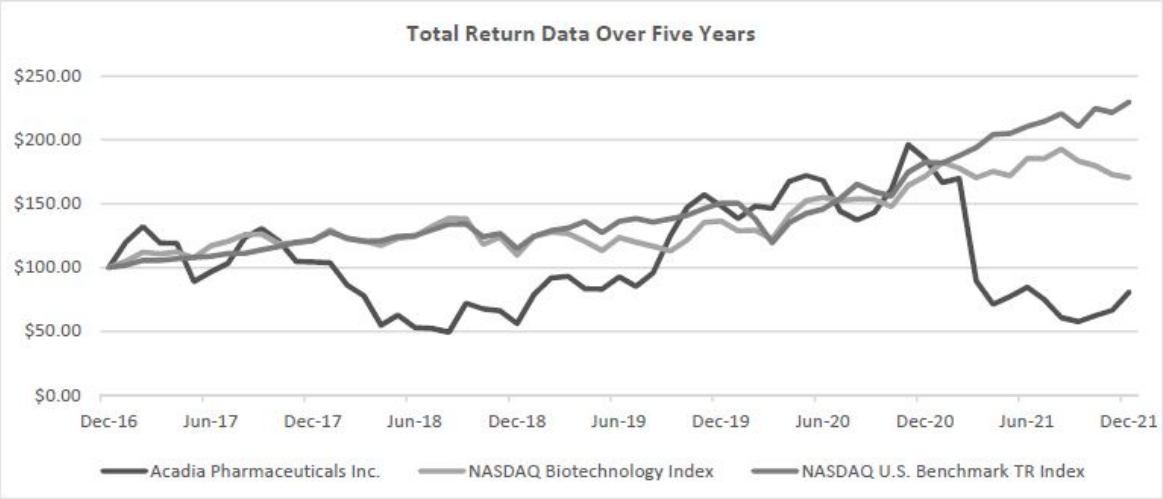
Item 5. ***Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.***

Our common stock is traded on the Nasdaq Global Select Market under the symbol "ACAD".

As of February 15, 2022, there were 161,203,748 shares of common stock outstanding held by approximately 33 stockholders of record. Many stockholders hold their shares in street name and we believe that there are approximately 61,000 beneficial owners of our common stock.

Performance Graph

The following graph shows a comparison of the total cumulative returns of an investment of $100 in cash from December 31, 2016 through December 31, 2021 in (i) our common stock, (ii) the Nasdaq Biotechnology Index, and (iii) the Nasdaq U.S. Benchmark TR Index. The comparisons in the graph are required by the SEC and are not intended to forecast or be indicative of the possible future performance of our common stock. The graph assumes that all dividends have been reinvested (to date, we have not declared any dividends).



Item 6. [Reserved]

Item 7. ***Management's Discussion and Analysis of Financial Condition and Results of Operations.***

The following discussion and analysis of our consolidated financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes included elsewhere in this report. Past operating results are not necessarily indicative of results that may occur in future periods. This discussion contains forward-looking statements, which involve a number of risks and uncertainties. Such forward-looking statements include statements about the benefits to be derived from NUPLAZID® (pimavanserin), trofinetide and from our drug candidates, the potential market opportunities for pimavanserin and our drug candidates, our strategy for the commercialization of NUPLAZID, our plans for exploring and developing pimavanserin for indications other than Parkinson's disease psychosis, our plans and timing with respect to seeking regulatory approvals, the potential commercialization of any of our drug candidates that receive regulatory approval, the progress, timing, results or implications of clinical trials and other development activities involving pimavanserin and our drug candidates, our strategy for discovering, developing and, if approved, commercializing drug candidates, our existing and potential future collaborations, our estimates of future payments, revenues and profitability, our estimates regarding our capital requirements, future expenses and need for additional financing, possible changes in legislation, and other statements that are not historical facts, including statements which may be preceded by the words "believes," "expects," "hopes," "may," "will," "plans," "intends," "estimates," "could," "should," "would," "continues," "seeks," "aims," "projects," "predicts," "pro forma," "anticipates," "potential" or similar words. In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon

information available to us as of the date of this report, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain. For forward-looking statements, we claim the protection of the Private Securities Litigation Reform Act of 1995. Readers of this report are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date on which they are made. We undertake no obligation to update or revise publicly any forward-looking statements. Forward-looking statements are not guarantees of performance. Actual results or events may differ materially from those anticipated in our forward-looking statements as a result of various factors, including those set forth under the section captioned "Risk Factors" elsewhere in this report. Information in the following discussion for a yearly period means for the year ended December 31 of the indicated year.

Overview

Background

We are a biopharmaceutical company focused on the development and commercialization of innovative medicines to address unmet medical needs in central nervous system disorders. We have a portfolio of product opportunities led by our novel drug, NUPLAZID (pimavanserin), which was approved by the FDA, in April 2016 for the treatment of hallucinations and delusions associated with PDP. We hold worldwide commercialization rights to pimavanserin. NUPLAZID is available in 34 mg capsules and 10 mg tablets dosage forms.

Since 2021, we have advanced our business and clinical studies through the following events:

- In March 2021, we initiated a Phase 2 study evaluating ACP-044 for the treatment of postoperative pain following bunionectomy surgery.
- In June 2021, we announced publication of open-label extension (OLE) data from patients experiencing hallucinations and delusions associated with PDP. The OLE efficacy analysis showed that patients previously on NUPLAZID 34 mg had a sustained efficacy response, and that patients who had been treated with investigational doses of 8.5 mg and 17 mg or placebo also showed an improvement in the symptoms of psychosis when switched to NUPLAZID 34 mg during OLE.
- In June 2021, we initiated an additional Phase 2 study evaluating ACP-044 for the treatment of pain associated with osteoarthritis.
- In December 2021, we announced positive top-line results from the pivotal Phase 3 LAVENDER study of trofinetide in Rett Syndrome. The study demonstrated a statistically significant improvement over placebo for both co-primary endpoints as well as key secondary endpoint.
- In January 2022, we entered into a license and collaboration agreement with Stoke to discover, develop and commercialize novel RNA-based medicines for the potential treatment of severe and rare genetic neurodevelopmental diseases of the CNS.
- In February 2022, we resubmitted to the FDA an sNDA for NUPLAZID for the treatment of hallucinations and delusions associated with ADP. In addition, based on the positive results from the Phase 3 LAVENDER study, we plan to submit to the FDA an NDA for trofinetide for the treatment of Rett syndrome around mid-year 2022.

We have incurred substantial operating losses since our inception due in large part to expenditures for our research and development activities and more recently for our sales and marketing activities related to the commercialization of NUPLAZID. As of December 31, 2021, we had an accumulated deficit of $2.2 billion. We expect to continue to incur operating losses for the next few years as we advance our programs and incur significant development and commercialization costs.

Impact of COVID-19 on our Business

On March 11, 2020, the World Health Organization declared a pandemic resulting from the disease known as COVID-19 caused by a novel strain of coronavirus, SARS-CoV-2. As a result of the pandemic, there have been changes in the practice of medical care and medical education. For example, many health care providers initially expanded their utilization of telemedicine to conduct patient visits, and in many regions within the United States the ability of our commercial and medical field teams to call upon medical clinics, hospitals, long-term care facilities and skilled nursing facilities was restricted or converted to virtual access. We continue to access our customers both in person and virtually. Currently, health care providers are conducting patient visits in-person and through telemedicine and our sales force has been able to call upon medical clinics, hospitals, long-term care facilities and skilled nursing facilities either in person in accordance with applicable regulatory guidance and local policies or virtually. Most medical congresses, an important means for medical education, are being conducted both in person and virtually and enrollment in clinical trials is being assessed based on local COVID-19 conditions and regional regulation and public health guidance.

In an effort to protect the health and safety of our employees and our stakeholders, we adopted recommended policies applicable to office-based employees such as working from home, limiting the number of employees on site, and reducing business travel. For our field-based commercial and medical affairs personnel, we have instituted a protocol to assess the safety of employees to conduct in-person interactions on a localized basis in accordance with applicable regulatory guidance and local policies.

Since the beginning of the pandemic, we have been able to provide an uninterrupted supply of NUPLAZID to patients. We are monitoring our supply chain closely and do not anticipate disruptions in our ability to continue delivering NUPLAZID to patients.

During 2021, sales of NUPLAZID were negatively impacted by ongoing conditions related to the pandemic, including a reduction in patient office visits, continuing reduced occupancy rates at long-term care facilities, and reduced access to healthcare professionals. While we observed incremental improvements in some of these factors during the second half of the year, their levels are still meaningfully below where they were pre-pandemic. It remains difficult to predict the duration of the pandemic's impact and the pace of recovery, and no assurances can be given that the pandemic will not continue to have additional negative impacts on our business, results of operations, financial condition and prospects.

Financial Operations Overview

Product and Collaborative Revenues

Net product sales consist of sales of NUPLAZID, our first and only commercial product to date. The FDA approved NUPLAZID in April 2016 and we launched the product in the United States in May 2016.

Cost of Product Sales

Cost of product sales consists of third-party manufacturing costs, freight, and indirect overhead costs associated with sales of NUPLAZID. Cost of product sales may also include period costs related to certain inventory manufacturing services, excess or obsolete inventory adjustment charges, unabsorbed manufacturing and overhead costs, and manufacturing variances.

License Fees and Royalties

License fees and royalties consist of milestone payments expensed or capitalized and subsequently amortized under our 2006 license agreement with the Ipsen Group. License fees and royalties also include royalties of 2% due to the Ipsen Group based upon net sales of NUPLAZID. This obligation terminated in October 2021.

Research and Development Expenses

Our research and development expenses have consisted primarily of fees paid to external service providers, salaries and related personnel expenses, facilities and equipment expenses, and other costs incurred related to pre-commercial product candidates. We charge all research and development expenses to operations as incurred. Our research and development activities have primarily focused on NUPLAZID (pimavanserin) which was approved by the FDA for the treatment of hallucinations and delusions associated with PDP in April 2016. We currently are responsible for all costs incurred in the ongoing development of pimavanserin and we expect to continue to make substantial investments in clinical studies of pimavanserin for indications other than PDP, including schizophrenia. In April 2021, the FDA issued a CRL in response to our sNDA seeking approval of pimavanserin for the treatment of hallucinations and delusions associated with DRP. While we have resubmitted our sNDA to the FDA for pimavanserin for the treatment of ADP, at this time, due to the risks in the regulatory and approval processes, it is difficult to estimate the costs we would incur for any additionally required development activities of pimavanserin in ADP and other subgroups of dementia-related psychosis, including work necessary to support the review of the sNDA. Additionally, in connection with the FDA approval of NUPLAZID, we committed to conduct post-marketing studies, including a randomized, placebo-controlled withdrawal study in patients treated with NUPLAZID and a randomized, placebo-controlled eight-week study or studies in predominantly frail and elderly patients that would add to the NUPLAZID safety database by exposing an aggregate of at least 500 patients to NUPLAZID. We will be responsible for all costs incurred for these post-marketing studies. While we intend to submit a NDA to the FDA for trofinetide for the treatment of Rett syndrome in mid-year 2022, at this time, due to the risks in the regulatory and approval processes, it is difficult to estimate with the costs we would incur for any additionally required development activities to support the submission and review of the NDA. We expect to incur increased research and development expenses as a result of our exclusive worldwide license agreement for the M1 PAM program, including ACP-319, and the research collaboration with Vanderbilt University, as well as our acquisition of CerSci and its ACP-044 product candidate and preclinical programs. We currently are responsible for all costs incurred in the development of trofinetide, ACP-044, ACP-319, the M1 PAM program and other preclinical programs, as well as milestone payments subject to achievement of development milestones.

We use external service providers to manufacture our product candidates and for the majority of the services performed in connection with the preclinical and clinical development of pimavanserin, trofinetide, ACP-044 and ACP-319. Historically, we have used our internal research and development resources, including our employees and discovery infrastructure, across several projects and many of our costs have not been attributable to a specific project. Accordingly, we have not reported our internal research and development costs on a project basis. To the extent that external expenses are not attributable to a specific project, they are included in other early stage programs.

The following table summarizes our research and development expenses for the years ended December 31, 2021, 2020, and 2019 (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Costs of external service providers:			
NUPLAZID (pimavanserin)	$ 73,696	$ 96,705	$ 124,749
Trofinetide	39,814	47,614	27,947
Early stage programs	35,964	14,691	4,714
Upfront and milestone payments*	10,999	72,666	1,375
Subtotal	160,473	231,676	158,785
Internal costs	56,973	56,140	49,067
Stock-based compensation	21,969	31,314	32,533
Total research and development expenses	$ 239,415	$ 319,130	$ 240,385

* Includes upfront and milestone consideration as well as transaction costs associated with acquired in-process research and development.

Although NUPLAZID was approved by the FDA for the treatment of hallucinations and delusions associated with PDP, at this time, due to the risks inherent in regulatory requirements and clinical development, we are unable to estimate with certainty the costs we will incur for the ongoing or additional development of pimavanserin in additional indications, including ADP and schizophrenia, and the development of trofinetide, ACP-044, ACP-319 and the M1 PAM program. Due to these same factors, we are unable to determine with any certainty the anticipated completion dates for our current research and development programs. Clinical development and regulatory approval timelines, probability of success, and development costs vary widely. While our current development efforts are primarily focused on advancing the development of pimavanserin in additional indications other than PDP, we anticipate that we will make determinations as to which programs to pursue and how much funding to direct to each program on an ongoing basis in response to the scientific and clinical success of each product candidate, as well as an ongoing assessment of the commercial potential of each opportunity and our financial position. We cannot forecast with any degree of certainty which product opportunities will be subject to future collaborative or licensing arrangements, when such arrangements will be secured, if at all, and to what degree any such arrangements would affect our development plans and capital requirements. Similarly, we are unable to estimate with certainty the costs we will incur for post-marketing studies that we committed to conduct in connection with FDA approval of NUPLAZID.

We expect our research and development expenses to increase and continue to be substantial as we conduct studies pursuant to our post-marketing commitments and pursue the development of pimavanserin in additional indications other than PDP, including our studies within schizophrenia, the development of ACP-044 for pain management, and the development of ACP-319. The lengthy process of completing clinical trials and supporting development activities and seeking regulatory approval for our product opportunities requires the expenditure of substantial resources. Any failure by us or delay in completing clinical trials, or in obtaining regulatory approvals, could cause our research and development expenses to increase and, in turn, have a material adverse effect on our results of operations.

Selling, General and Administrative Expenses

Our selling, general and administrative expenses consist of salaries and other related costs, including stock-based compensation expense, for our commercial personnel, including our specialty sales force, our medical education professionals, and our personnel serving in executive, finance, business development, and business operations functions. Also included in selling, general and administrative expenses are fees paid to external service providers to support our commercial activities associated with NUPLAZID, professional fees associated with legal and accounting services, costs associated with patents and patent applications for our intellectual property and charitable donations to independent charitable foundations that support Parkinson's disease patients generally. We expect our selling, general and administrative expenses to increase in future periods to support commercial activities associated with NUPLAZID and our further development of pimavanserin in additional indications other than PDP.

Critical Accounting Policies and Estimates

A summary of the significant accounting policies is provided in Note 2 to our Consolidated Financial Statements.

The preparation of financial statements in accordance with U.S. generally accepted accounting principles (GAAP) requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. We evaluate our estimates on an ongoing basis. Our estimates are based on historical experience and on various other assumptions and factors that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities and the reported amounts of revenues and expenses that are not readily apparent from other sources. Actual results may differ from those estimates under different assumptions and conditions.

Management considers an accounting estimate to be critical if:

- it requires a significant level of estimation uncertainty; and
- changes in the estimate are reasonably likely to have a material effect on our financial condition or results of operations.

We believe the following critical accounting policies and estimates describe the more significant judgments and estimates used in the preparation of our consolidated financial statement.

Product Sales, Net

We sale our product through SPs and SDs. SPs dispense product to a patient based on the fulfillment of a prescription and SDs sell product to government facilities, long-term care pharmacies, or in-patient hospital pharmacies. Product shipping and handling costs are included in cost of product sales.

We recognize revenue from product sales at the net sales price (the “transaction price”) which includes estimates of variable consideration for which reserves are established and reflects each of these as either a reduction to the related account receivable or as an accrued liability, depending on how the amount payable is settled. Overall, these reserves reflect our best estimates of the amount of consideration to which we are entitled based on the terms of the contract. Actual amounts of consideration ultimately received may differ from our estimates. If actual results in the future vary from estimates, we may need to adjust our estimates, which would affect net revenue in the period of adjustment. The following sales discounts and allowances involve a substantial degree of judgment:

Rebates: Allowances for rebates include mandated discounts under the Medicaid Drug Rebate Program and the Medicare Part D prescription drug benefit. Rebates are amounts owed after the final dispensing of the product to a benefit plan participant and are based upon contractual agreements with, or statutory requirements pertaining to, Medicaid and Medicare benefit providers. The allowance for rebates is based on statutory discount rates and expected utilization. Our estimates for expected utilization of rebates is based on historical data received from the SPs and SDs since product launch. Rebates are generally invoiced and paid in arrears so that the accrual balance consists of an estimate of the amount expected to be incurred for the current quarter’s activity, plus an accrual balance for prior quarters’ unpaid rebates still estimated to be incurred.

Chargebacks: Chargebacks are discounts and fees that relate to contracts with government and other entities purchasing from the SDs at a discounted price. The SDs charge back to us the difference between the price initially paid by the SDs and the discounted price paid to the SDs by these entities. We also incur group purchasing organization fees for transactions through certain purchasing organizations. We estimate sales with these entities and accrue for anticipated chargebacks and organization fees, based on the applicable contractual terms.

Research and Development Accruals

We estimate certain costs and expenses and accrue for these liabilities as part of our process of preparing financial statements. Examples of areas in which subjective judgments may be required include, among other things, costs associated with services provided by contract organizations for preclinical development, manufacturing of our product candidates and clinical trials, and personnel related expenses. We accrue for costs incurred as the services are being provided by monitoring the status of the trial or services provided, and the invoices received from our external service providers. In the case of clinical trials, a portion of the estimated cost normally relates to the projected cost to treat a patient in the trials, and this cost is recognized based on the number of patients enrolled in the trial. Other indirect costs are generally recognized on a straight-line basis over the estimated period of the study. As actual costs become known to us, we adjust our accruals. To date, our estimates have not differed materially from the actual costs incurred. However, subsequent changes in estimates may result in a material change in our accruals, which could also materially affect our balance sheet and results of operations

Stock-Based Compensation

The fair value of each employee stock option and each employee stock purchase plan right granted is estimated on the grant date under the fair value method using the Black-Scholes valuation model, which requires us to make a number of assumptions including the estimated expected life of the award and related volatility. The fair value of restricted stock units is estimated based on the market price of our common stock on the date of grant. The estimated fair values of stock options, purchase plan rights, and regular restricted stock units are then expensed over the vesting period. For restricted stock units requiring satisfaction of both market and service conditions, the estimated fair values are generally expensed over the longest of the explicit, implicit and derived service periods. Performance-based stock awards vest upon the achievement of certain pre-defined company-specific performance-based criteria. Expense related to these performance-based stock awards is generally recognized ratably over the expected performance period once the pre-defined performance-based criteria for vesting becomes probable.

Results of Operations

Fluctuations in Operating Results

Our results of operations have fluctuated significantly from period to period in the past and are likely to continue to do so in the future. We anticipate that our quarterly and annual results of operations will be impacted for the foreseeable future by several factors, including the progress and timing of expenditures related to our commercial activities associated with NUPLAZID and the extent to which we generate revenue from product sales, our development of pimavanserin in additional indications other than PDP, our development of trofinetide, ACP-044, ACP-319, and the M1 PAM program, and the progress and timing of expenditures related to studies of NUPLAZID in PDP pursuant to our post-marketing commitments. Further, we expect our sales allowances to vary from quarter to quarter due to fluctuations in our Medicare Part D Coverage Gap liability and the volume of purchases eligible for government mandated discounts and rebates, as well as changes in discount percentages that may be impacted by potential future price increases and other factors. We cannot predict with certainty what the full impact of the COVID-19 pandemic may have on our business, results of operations, financial condition and prospects. Due to these fluctuations, we believe that the period-to-period comparisons of our operating results are not a good indication of our future performance.

Comparison of the Years Ended December 31, 2021 and 2020

Product Sales, Net

Net product sales, comprised of NUPLAZID, were $484.1 million and $441.8 million in 2021 and 2020, respectively. Net product sales for the year ended December 31, 2021 increased as compared to the year ended December 31, 2020 primarily due to a higher average gross selling price of NUPLAZID in 2021 as compared to 2020 as well as the growth in NUPLAZID unit sales of approximately 3% in 2021 as compared to 2020.

The following table provides a summary of activity with respect to our sales allowances and accruals for the year ended December 31, 2021 (in thousands):

	Distribution Fees, Discounts & Chargebacks	Co-Pay Assistance	Rebates, Data Fees & Returns	Total
Balance at December 31, 2020	$ 4,221	$ (152)	$ 14,116	$ 18,185
Provision related to current period sales	72,011	1,794	40,490	114,295
Credits/payments for current period sales	(63,544)	(1,996)	(24,773)	(90,313)
Credits/payments for prior period sales	(4,221)	152	(14,116)	(18,185)
Balance at December 31, 2021	$ 8,467	$ (202)	$ 15,717	$ 23,982

Cost of Product Sales

Cost of product sales was $10.8 million and $10.2 million in 2021 and 2020, respectively, or approximately 2% of net product sales, respectively. The cost of product sales as a percentage of net sales stayed flat during 2021 as compared to 2020.

License Fees and Royalties

License fees and royalties were $8.3 million and $10.3 million in 2021 and 2020, respectively, and include royalties due to the Ipsen Group of two percent of net sales of NUPLAZID and amortization related to the milestone paid to the Ipsen Group upon FDA approval of NUPLAZID in 2016. The royalty obligation terminated in October 2021 which was the primary reason for the decrease in license fees and royalties during 2021 as compared to 2020.

Research and Development Expenses

Research and development expenses decreased to $239.4 million in 2021, including $22.0 million in stock-based compensation, from $319.1 million in 2020, including $31.3 million in stock-based compensation. The decrease in research and development expenses was due to a decrease of $71.2 million in external costs and a decrease of $8.4 million in personnel and related costs resulting from attrition. The decrease in external costs was primarily due to the $52.8 million in upfront consideration and transaction costs paid for the acquisition of CerSci and $10.0 million upfront payment to Vanderbilt University for the M1 PAM program in 2020.

Selling, General and Administrative Expenses

Selling, general and administrative expenses increased to $396.0 million in 2021, including $40.4 million in stock-based compensation, from $388.7 million in 2020, including $50.5 million in stock-based compensation. The increase in selling, general and administrative expenses was primarily due to an increase of $16.4 million in personnel and related costs, partially offset by a decrease of $10.1 million in stock compensation expense.

Comparison of the Years Ended December 31, 2020 and 2019

Product Sales, Net

Net product sales, comprised of NUPLAZID, were $441.8 million and $339.1 million in 2020 and 2019, respectively. Net product sales for the year ended December 31, 2020 increased as compared to the year ended December 31, 2019 primarily due to growth in NUPLAZID unit sales of approximately 18% in 2020 as compared to 2019. Also contributing to the increase was a higher average gross selling price of NUPLAZID in 2020 as compared to 2019.

The following table provides a summary of activity with respect to our sales allowances and accruals for the year ended December 31, 2020 (in thousands):

	Distribution Fees, Discounts & Chargebacks	Co-Pay Assistance	Rebates, Data Fees & Returns	Total
Balance at December 31, 2019	$ 2,576	$ 316	$ 11,326	$ 14,218
Provision related to current period sales	51,684	1,759	36,745	90,188
Credits/payments for current period sales	(47,463)	(1,911)	(22,629)	(72,003)
Credits/payments for prior period sales	(2,576)	(316)	(11,326)	(14,218)
Balance at December 31, 2020	$ 4,221	$ (152)	$ 14,116	$ 18,185

Cost of Product Sales

Cost of product sales was $10.2 million and $11.3 million in 2020 and 2019, respectively, or approximately 2% and 3% of net product sales. The cost of product sales as a percentage of net sales decreased during 2020 as compared to 2019 due to higher manufacturing levels, resulting in higher inventory cost absorption and increased sales volume at a higher average gross selling price in 2020.

License Fees and Royalties

License fees and royalties were $10.3 million and $8.3 million in 2020 and 2019, respectively, and include royalties due to the Ipsen Group of two percent of net sales of NUPLAZID and amortization related to the milestone paid to the Ipsen Group upon FDA approval of NUPLAZID in 2016. The increase in license fees and royalties was primary due to the increase in sales volume during 2020.

Research and Development Expenses

Research and development expenses increased to $319.1 million in 2020, including $31.3 million in stock-based compensation, from $240.4 million in 2019, including $32.5 million in stock-based compensation. The increase in research and development expenses was due to an increase of $72.9 million in external costs and an increase of $5.8 million in personnel and related costs. The increase in external costs was primarily due to the $52.8 million in upfront consideration and transaction costs paid for the acquisition of CerSci and $10.0 million upfront payment to Vanderbilt University for the M1 PAM program.

Selling, General and Administrative Expenses

Selling, general and administrative expenses increased to $388.7 million in 2020, including $50.5 million in stock-based compensation, from $325.6 million in 2019, including $46.8 million in stock-based compensation. The increase in selling, general and administrative expenses was due to an increase of $38.0 million in external costs and an increase of $25.1 million in personnel and related costs, including an increase of $3.7 million in stock compensation expense. The increase during the year end December 31, 2020 as compared to 2019 was primarily due to increased advertising and promotional costs, dementia-related psychosis launch preparation expenses, as well as an increase in personnel and related costs.

Liquidity and Capital Resources

We have funded our operations primarily through sales of our equity securities, payments received under our collaboration agreements, debt financings, interest income, and, since 2016, with revenues from sales of NUPLAZID. We anticipate that the level of cash used in our operations will increase in future periods in order to fund our ongoing and planned commercial activities for NUPLAZID, our ongoing and planned development activities for pimavanserin in additional indications other than PDP, studies to be conducted pursuant to our post-marketing commitments and our ongoing and planned development activities for trofinetide for the treatment of Rett syndrome, ACP-044 for pain management, and for various M1 PAM compounds, including ACP-319, under the agreement with Vanderbilt University. We expect that our cash, cash equivalents, and investment securities will be sufficient to fund our planned operations through at least the next 12 months.

We may require significant additional financing in the future to fund our operations. Our future capital requirements will depend on, and could increase significantly as a result of, many factors, including:

- the progress in, and the costs of, our ongoing and planned development activities for pimavanserin, post-marketing studies for NUPLAZID to be conducted over the next several years, and ongoing and planned commercial activities for NUPLAZID;
- the costs of our development activities for trofinetide;
- the costs of our development activities for ACP-044;
- the costs of our development activities for ACP-319
- the costs of our development activities for the M1 PAM program;
- the costs of commercializing NUPLAZID, including the maintenance and development of our sales and marketing capabilities;
- the costs of establishing, or contracting for, sales and marketing capabilities for other product candidates;
- the amount of U.S. product sales from NUPLAZID;
- the costs of preparing applications for regulatory approvals for NUPLAZID in jurisdictions other than the U.S., and in additional indications other than PDP and for other product candidates, as well as the costs required to support review of such applications;
- the costs of manufacturing and distributing NUPLAZID for commercial use in the U.S.;
- our ability to obtain regulatory approval for, and subsequently generate product sales from, NUPLAZID in jurisdictions other than the U.S. or in additional indications other than PDP, or from trofinetide, ACP-044, ACP-319 and other product candidates;
- the costs of acquiring additional product candidates or research and development programs;

- the scope, prioritization and number of our research and development programs;
- the ability of our collaborators and us to reach the milestones and other events or developments triggering payments under our collaboration or license agreements, or our collaborators' ability to make payments under these agreements;
- our ability to enter into new collaboration and license agreements;
- the extent to which we are obligated to reimburse collaborators or collaborators are obligated to reimburse us for costs under collaboration agreements;
- the costs involved in filing, prosecuting, enforcing, and defending patent claims and other intellectual property rights;
- the costs of maintaining or securing manufacturing arrangements for clinical or commercial production of pimavanserin, trofinetide or other product candidates; and
- the costs associated with litigation, including the costs incurred in defending against any product liability claims that may be brought against us related to NUPLAZID.

Unless and until we can generate significant cash from our operations, we expect to satisfy our future cash needs through our existing cash, cash equivalents and investment securities, public or private sales of our securities, debt financings, strategic collaborations, or by licensing all or a portion of our product candidates or technology. In the past, periods of turmoil and volatility in the financial markets have adversely affected the market capitalizations of many biotechnology companies, and generally made equity and debt financing more difficult to obtain. For example, due to the COVID-19 pandemic and actions taken to slow its spread, the global credit and financial markets have experienced extreme volatility and disruptions, including diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. These events, coupled with other factors, may limit our access to additional financing in the future. We cannot be certain that additional funding will be available to us on acceptable terms, or at all. If adequate funds are not available when needed, we will be required to delay, reduce the scope of, or eliminate one or more of our research or development programs or our commercialization efforts. We also may be required to relinquish greater or all rights to product candidates at an earlier stage of development or on less favorable terms than we would otherwise choose. Additional funding, if obtained, may significantly dilute existing stockholders and could negatively impact the price of our stock.

Material Cash Requirements

Our material cash requirements in the short and long term consist of the operational, manufacturing, and capital expenditures, a portion of which contain contractual or other obligations. We plan to fund our material cash requirements with our current financial resources together with our anticipated receipts from product sales. On a long-term basis, we manage future cash requirements relative to our long-term business plans.

Our primary uses of cash and operating expenses relate to paying employees and consultants, administering clinical trials, marketing our products, and providing technology and facility infrastructure to support our operations. We also make investments in our office and laboratory facilities to enable continued expansion of our business.

The following is a summary of our long-term contractual obligations as of December 31, 2021 (in thousands):

	Total	Less than 1 Year	1-3 Years	3-5 Years	More than 5 Years
Operating leases	$ 77,815	$ 8,520	$ 16,665	$ 16,074	$ 36,556
Other long-term contractual obligations	3,235	1,235	2,000	—	—
Total	$ 81,050	$ 9,755	$ 18,665	$ 16,074	$ 36,556

In addition to operating leases, we enter into certain other long-term commitments for goods and services that are outstanding for periods greater than one year. To the extent these long-term commitments are noncancelable, they are reflected in the above table. We also enter into short-term agreements with various vendors and suppliers of goods and services in the normal course of operations through purchase orders or other documentation, or that are undocumented except for an invoice. Such short-term agreements are generally outstanding for periods less than a year and are settled by cash payments upon delivery of goods and services. The nature of the work being conducted under these agreements is such that, in most cases, the services may be stopped on short notice. In such event, we would not be liable for the full amount of the agreement and therefore these amounts are not reflected in the above table.

We have entered into various collaboration, licensing and merger agreements which generally include upfront license fees, development and commercial milestone payments upon achievement of certain clinical and commercial development and annual net sales milestones, as well as royalties calculated as a percentage of product revenues, with rates that vary by agreement. As of December 31, 2021, we may be required to make milestone payments up to $2.2 billion in the aggregate. These payments are contingent upon achieving future development, regulatory and commercial milestones. We are also required to make royalty payments in connection with the sale of products developed under those agreements. We have not included any such milestone or royalty payments in the above table. In January 2022, we entered into a license and collaboration agreement with Stoke to discover, develop and commercialize novel RNA-based medicines for the potential treatment of severe and rare genetic neurodevelopmental diseases of the CNS. Under the terms of the agreement, we may be required to pay up to $907.5 million in milestone payments based on the achievement of certain clinical and commercial development and annual net sales milestones.

Cash Flows

At December 31, 2021, we had $520.7 million in cash, cash equivalents, and investment securities, compared to $632.0 million at December 31, 2020. This $111.3 million decrease in cash, cash equivalents, and investment securities during 2021 was primarily due to net cash used in operating activities, offset in part by cash proceeds from the exercise of employee stock options.

Net cash used in operating activities decreased to $125.7 million in 2021 compared to $136.2 million in 2020 and $151.1 million in 2019. The decrease in net cash used in operating activities in 2021 relative to 2020 was due to an increase in our net revenues as well as decreased research and development costs and sales and marketing costs. The decrease in net cash used in operating activities in 2020 relative to 2019 was due to an increase in our net revenues, partially offset by additional research and development costs, including the upfront license fees and payments and upfront and closing costs paid for the acquisition of CerSci, and sales and marketing costs.

Net cash used in investing activities totaled $71.1 million in 2021 compared to net cash provided by investing activities of $192.5 million in 2020 and net cash used in investing activities of $165.8 million in 2019. The increase in net cash used in investing activities in 2021 compared to 2020 was primarily due to increased net purchases of investment securities. The increase in net cash provided by investing activities in 2020 compared to 2019 was primarily due to increased net maturities of investment securities.

Net cash provided by financing activities decreased to $18.2 million in 2021 compared to $81 million in 2020 and $371.8 million in 2019. The decrease in net cash provided by financing activities in 2021 relative to 2020 was primarily due to a decrease in proceeds resulting from the exercise of employee stock options. The decrease in net cash provided by financing activities in 2020 relative to 2019 was attributable primarily to the follow-on public offering in September 2019, which resulted in net proceeds of $271.5 million.

Off-Balance Sheet Arrangements

To date, we have not had any relationships with unconsolidated entities or financial partnerships, such as entities referred to as structured finance or special purpose entities, which are established for the purpose of facilitating off-balance sheet arrangements or other contractually narrow or limited purposes. As such, we are not materially exposed to any financing, liquidity, market or credit risk that could arise if we had engaged in these relationships.

Recent Accounting Pronouncements

See Item 15 of Part IV, “Notes to Consolidated Financial Statements—Note 2—Summary of Significant Accounting Policies.”

Item 7A. ***Quantitative and Qualitative Disclosures About Market Risk***

Interest Rate Risk

We invest our excess cash in investment-grade, interest-bearing securities. The primary objective of our investment activities is to preserve principal and liquidity. To achieve this objective, we invest in money market funds. U.S. treasury notes, and high quality marketable debt instruments of corporations and government sponsored enterprises with contractual maturity dates of generally less than one year. All investment securities have a credit rating of at least Aa3/AA- or better, or P-1/A-1 or better, as determined by Moody's Investors Service or Standard & Poor's. We do not have any direct investments in auction-rate securities or securities that are collateralized by assets that include mortgages or subprime debt. If a 10 percent change in interest rates were to have occurred on December 31, 2021, this change would not have had a material effect on the fair value of our investment portfolio as of that date.

Item 8. ***Financial Statements and Supplementary Data.***

The consolidated financial statements required pursuant to this item are included in Item 15 of this report and are presented beginning on page F-1.

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

None.

Item 9A. ***Controls and Procedures.***

Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our periodic and current reports that we file with the SEC is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer (our principal executive officer and principal financial officer, respectively), as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognized that any controls and procedures, no matter how well designed and operated, can provide only reasonable and not absolute assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures. In addition, the design of any system of controls is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions; over time, controls may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

As of December 31, 2021, we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures, as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of December 31, 2021.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States of America.

As of December 31, 2021, our management assessed the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in Internal Control-Integrated Framework (2013). Based on this assessment, management, under the supervision and with the participation of our Chief Executive Officer and Chief Financial Officer, concluded that, as of December 31, 2021, our internal control over financial reporting was effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2021 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in its report, which is included herein.

Changes in Internal Control Over Financial Reporting

An evaluation was also performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of any changes in our internal control over financial reporting that occurred during our last fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. That evaluation did not identify any change in our internal control over financial reporting that occurred during our latest fiscal quarter and that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of
Acadia Pharmaceuticals Inc.

Opinion on Internal Control Over Financial Reporting

We have audited Acadia Pharmaceuticals Inc.'s internal control over financial reporting as of December 31, 2021, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Acadia Pharmaceuticals Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2021, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of Acadia Pharmaceuticals Inc. as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive loss, cash flows and stockholders' equity for each of the three years in the period ended December 31, 2021, and the related notes and the financial statement schedule listed in the Index at Item 15(a)2 and our report dated February 28, 2022 expressed an unqualified opinion thereon.

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 Report on Internal Control 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/ Ernst & Young LLP

San Diego, California
February 28, 2022

Item 9B. ***Other Information***

None.

PART III

Item 10. ***Directors, Executive Officers and Corporate Governance.***

The information required by this Item and not set forth below will be set forth in the section headed "—Election of Directors" and "Information Regarding the Board of Directors and Corporate Governance" in our definitive Proxy Statement for our 2022 Annual Meeting of Stockholders to be filed with the SEC by April 30, 2022 (our "Proxy Statement") and is incorporated in this report by reference.

We have adopted a code of ethics for directors, officers (including our principal executive officer, principal financial officer and principal accounting officer) and employees, known as the Code of Business Conduct and Ethics. The Code of Business Conduct and Ethics is available on our website at *http://www.acadia-pharm.com* under the Corporate Governance section of our Investors page. We will promptly disclose on our website (i) the nature of any amendment to the policy that applies to our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions and (ii) the nature of any waiver, including an implicit waiver, from a provision of the policy that is granted to one of these specified individuals, the name of such person who is granted the waiver and the date of the waiver. Stockholders may request a free copy of the Code of Business Conduct and Ethics from our compliance department c/o Acadia Pharmaceuticals Inc., 12830 El Camino Real, Suite 400, San Diego, CA 92130.

Item 11. ***Executive Compensation.***

The information required by this Item will be set forth in the section headed "Executive Compensation" in our Proxy Statement and is incorporated in this report by reference.

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

The information required by this Item will be set forth in the section headed "Security Ownership of Certain Beneficial Owners and Management" in our Proxy Statement and is incorporated in this report by reference.

Information regarding our equity compensation plans will be set forth in the section headed "Executive Compensation" in our Proxy Statement and is incorporated in this report by reference.

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

The information required by this Item will be set forth in the section headed "Transactions With Related Persons" in our Proxy Statement and is incorporated in this report by reference.

Item 14. ***Principal Accountant Fees and Services.***

The information required by this Item will be set forth in the section headed "—Ratification of Selection of Independent Registered Public Accounting Firm" in our Proxy Statement and is incorporated in this report by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules.

(a) Documents filed as part of this report.

1. The following financial statements of Acadia Pharmaceuticals Inc. and Report of Ernst & Young LLP, Independent Registered Public Accounting Firm, are included in this report:

	Page Number
Report of Independent Registered Public Accounting Firm (PCAOB ID: 42)	F-1
Consolidated Balance Sheets	F-3
Consolidated Statements of Operations	F-4
Consolidated Statements of Comprehensive Loss	F-5
Consolidated Statements of Cash Flows	F-6
Consolidated Statements of Stockholders' Equity	F-7
Notes to Consolidated Financial Statements	F-8

2. List of financial statement schedules:

Schedule II – Valuation and Qualifying Accounts

Schedules not listed above have been omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

3. List of Exhibits required by Item 601 of Regulation S-K. See part (b) below.

(b) Exhibits.

Exhibit Number	Description
3.1	Amended and Restated Certificate of Incorporation, as Amended (incorporated by reference to Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q, filed August 6, 2015).
3.2	Certificate of Amendment of Amended and Restated Certificate of Incorporation (incorporated by reference to Exhibit 3.2 to the Registrant's Annual Report on Form 10-K, filed February 25, 2021).
3.3	Amended and Restated Bylaws (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K, filed September 12, 2013).
4.1	Form of common stock certificate of the Registrant (incorporated by reference to Exhibit 4.1 to Registration Statement No. 333-52492).
4.2	Form of Amended and Restated Warrant to Purchase Common Stock (incorporated by reference to Exhibit 4.2 to the Registrant's Annual Report on Form 10-K, filed February 26, 2019).
4.3	Description of the Registrant's Common Stock (incorporated by reference to Exhibit 4.3 to the Registrant's Annual Report on Form 10-K, filed February 27, 2020).
10.1[a]	Form of Indemnity Agreement for directors and officers (incorporated by reference to Exhibit 10.1 to Registration Statement No. 333-113137).
10.2[a]	2004 Equity Incentive Plan and forms of agreement thereunder (incorporated by reference to Exhibit 10.3 to Registration Statement No. 333-113137).
10.3[a]	2010 Equity Incentive Plan, as amended (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K, filed June 28, 2019).
10.4[a]	Forms of agreement under the 2010 Equity Incentive Plan (incorporated by reference to Exhibit 10.4 to the Registrant's Annual Report on Form 10-K, filed February 29, 2016).

10.5[a]	2004 Employee Stock Purchase Plan, as amended (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K, filed June 29, 2010).
10.6[a]	Offerings under the 2004 Employee Stock Purchase Plan, as amended (incorporated by reference to Exhibit 10.6 to the Registrant's Annual Report on Form 10-K, filed February 28, 2017).
10.7[a]	Employment Agreement, dated September 1, 2015, between the Registrant and Stephen Davis (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K, filed September 3, 2015).
10.8[a]	Employment Offer Letter, dated October 28, 2015, between the Registrant and Srdjan Stankovic (incorporated by reference to Exhibit 10.10 to the Registrant's Annual Report on Form 10-K, filed February 29, 2016).
10.9[a]	Employment Offer Letter, dated June 26, 2018, between the Registrant and Brendan Teehan.
10.10[a]	Employment Offer Letter, dated July 2, 2018, between the Registrant and Austin D. Kim (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, filed November 6, 2018).
10.11[a]	Employment Offer Letter, dated April 28, 2020, between the Registrant and Mark Schneyer.
10.12[a]	Non-Employee Director Compensation Policy (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K, filed June 29, 2020).
10.13[a]	Management Severance Benefit Plan (incorporated by reference to Exhibit 99.1 to the Registrant's Current Report on Form 8-K, filed December 15, 2015).
10.14[a]	Amended and Restated Change in Control Severance Benefit Plan (incorporated by reference to Exhibit 99.2 to the Registrant's Current Report on Form 8-K, filed December 15, 2015).
10.15[b]	Master Manufacturing Services Agreement and Product Agreement, dated August 3, 2015, by and between the Registrant and Patheon Pharmaceuticals Inc. (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, filed November 5, 2015).
10.16[b]	First Amendment to Product Agreement, dated April 25, 2016, by and between the Registrant and Patheon Pharmaceuticals Inc. (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, filed August 4, 2016).
10.17[b]	Second Amendment to Product Agreement, dated October 6, 2016, by and between the Registrant and Patheon Pharmaceuticals Inc. (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly Report on Form 10-Q, filed November 7, 2016).
10.18[b]	Third Amendment to Product Agreement, dated December 11, 2017, by and between the Registrant and Patheon Pharmaceuticals Inc (incorporated by reference to Exhibit 10.19 to the Registrant's Annual Report on Form 10-K, filed February 27, 2018.
10.19[b]	Master Services Agreement, dated December 15, 2016, by and between Acadia Pharmaceuticals GmbH and Siegfried AG and its affiliates, and Attachment #1, Attachment #2 and Attachment #3 (incorporated by reference to Exhibit 10.20 to the Registrant's Annual Report on Form 10-K, filed February 28, 2017).
10.20[b]	Change Order #1 to Master Services Agreement Attachment #1, dated January 3, 2017, by and between Acadia Pharmaceuticals GmbH and Siegfried AG (incorporated by reference to Exhibit 10.21 to the Registrant's Annual Report on Form 10-K, filed February 28, 2017).
10.21[b]	Attachment #4, Attachment #5 and Attachment #6, each dated May 12, 2017, to the Master Services Agreement, dated December 15, 2016, by and between Acadia Pharmaceuticals GmbH and Siegfried AG and its affiliates (incorporated by reference to Exhibit 10.3 to the Registrant's Quarterly Report on Form 10-Q, filed August 8, 2017).
10.22[c]	Attachment #7, dated September 30, 2020, to the Master Services Agreement, dated December 15, 2016, by and between Acadia Pharmaceuticals GmbH and Siegfried AG and its affiliates (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly report on Form 10-Q, filed November 4, 2020).
10.23	Registration Rights Agreement, dated January 6, 2016, between the Registrant and the investors listed on Schedule A thereto (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K, filed January 7, 2016).

10.24	Assignment of Brann Intellectual Property Rights, dated January 29, 1997, by Mark R. Brann in favor of the Registrant (incorporated by reference to Exhibit 10.17 to Registration Statement No. 333-52492).
10.25[b]	License Agreement, dated August 6, 2018, by and between the Registrant and Neuren Pharmaceuticals Ltd. (incorporated by reference to Exhibit 10.26 to the Registrant's Annual Report on Form 10-K, filed February 27, 2019).
10.26[b]	Lease Agreement, effective October 4, 2018, by and between the Registrant and Kilroy Realty, L.P. (incorporated by reference to Exhibit 10.27 to the Registrant's Annual Report on Form 10-K, filed February 27, 2019).
10.27[c]	First Amendment to Office Lease, dated December 23, 2019, between the Registrant and Kilroy Realty, L.P. (incorporated by reference to Exhibit 10.1 to the Registrant's Quarterly report on Form 10-Q, filed May 8, 2020).
10.28[c]	Second Amendment to Office Lease, dated March 12, 2020, between the Registrant and Kilroy Realty, L.P. (incorporated by reference to Exhibit 10.2 to the Registrant's Quarterly report on Form 10-Q, filed May 8, 2020).
21.1	List of subsidiaries of the Registrant.
23.1	Consent of Independent Registered Public Accounting Firm.
24.1	Power of Attorney (see signature page hereto).
31.1	Certification of Stephen Davis, Chief Executive Officer, pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2	Certification of Mark Schneyer, Executive Vice President and Chief Financial Officer, pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1	Certification of Stephen Davis, Chief Executive Officer, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2	Certification of Mark Schneyer, Executive Vice President and Chief Financial Officer, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial statements from this Annual Report, formatted in iXBRL (Inline Extensible Business Reporting Language), are filed herewith: (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations, (iii) Consolidated Statements of Comprehensive Loss, (iv) Consolidated Statements of Cash Flows, (v) Consolidated Statements of Stockholders' Equity, and (vi) Notes to Consolidated Financial Statements.
104	Cover Page Interactive Data File (formatted as inline XBRL and contained in Exhibit 101)

[a] Indicates management contract or compensatory plan or arrangement.

[b] We have requested or received confidential treatment of certain portions of this agreement, which have been omitted and filed separately with the SEC pursuant to Rule 406 under the Securities Act of 1933, as amended, or Rule 24b-2 of the Securities Exchange Act of 1934, as amended.

[c] Certain portions of this exhibit (indicated by "[…***…]") have been omitted pursuant to confidential treatment.

Item 16. ***Form 10-K Summary***

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities and Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

ACADIA PHARMACEUTICALS INC.

Date: February 28, 2022

/s/ STEPHEN R. DAVIS

Stephen R. Davis
Chief Executive Officer
(on behalf of the registrant and as the registrant's Principal Executive Officer)

KNOW ALL PERSONS BY THESE PRESENTS, that each individual whose signature appears below constitutes and appoints Stephen R. Davis his true and lawful attorney-in-fact and agent, with full power of substitution, for him and in his or her name, place and stead, in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto and all documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agent full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorney-in-fact and agent, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

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

Signature	Title	Date
/s/ STEPHEN R. DAVIS **Stephen R. Davis**	Chief Executive Officer and Director (Principal Executive Officer)	February 28, 2022
/s/ MARK C. SCHNEYER **Mark C. Schneyer**	Executive Vice President and Chief Financial Officer (Principal Financial Officer)	February 28, 2022
/s/ JAMES K. KIHARA **James K. Kihara**	Vice President, Chief Accounting Officer and Controller (Principal Accounting Officer)	February 28, 2022
/s/ STEPHEN R. BIGGAR **Stephen R. Biggar**	Chairman of the Board	February 28, 2022
/s/ JULIAN C. BAKER **Julian C. Baker**	Director	February 28, 2022
/s/ LAURA A. BREGE **Laura A. Brege**	Director	February 28, 2022
/s/ JAMES M. DALY **James M. Daly**	Director	February 28, 2022
/s/ ELIZABETH A. GAROFALO **Elizabeth A. Garofalo**	Director	February 28, 2022
/s/ EDMUND P. HARRIGAN **Edmund P. Harrigan**	Director	February 28, 2022
/s/ DANIEL B. SOLAND **Daniel B. Soland**	Director	February 28, 2022

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of
Acadia Pharmaceuticals Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Acadia Pharmaceuticals Inc. (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations, comprehensive loss, cash flows and stockholders' equity for each of the three years in the period ended December 31, 2021, and the related notes and the financial statement schedule listed in the Index at Item 15(a)2 (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

We also have 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, 2021, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework), and our report dated February 28, 2022 expressed an unqualified opinion thereon.

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 matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Allowance for Medicare Part D rebates

Description of the Matter As more fully described in Note 2 to the consolidated financial statements, the Company recognizes revenue from product sales at the net sales price (the "transaction price") which includes estimates of variable consideration for which reserves for sales discounts and allowances are established. Estimated sales discounts and allowances were $24.0 million as of December 31, 2021. The product sales, adjusted for the sales discounts and allowances, reflect the Company's best estimates of the amount of consideration to which the Company is entitled based on the terms of the contract. The most significant category within the Company's sales discounts and allowances are rebates for Medicare Part D. The Medicare Part D rebates are mandated discounts under the Medicare Part D prescription drug benefit, owed after the final dispensing of the product to a benefit plan participant and are based upon statutory requirements. The estimate for the Medicare Part D rebates is based on expected utilization and estimated payor mix of the Company's gross sales. The Company's estimates of payor mix and expected utilization of Medicare Part D rebates are based on historical data received from the specialty pharmacies (SPs) and specialty distributors (SDs) since product launch.

Auditing the Company's estimate for Medicare Part D rebates is complex, requires significant judgment, uses subjective assumptions, and the amounts involved are material to the financial statements. The subjective assumptions include estimates of expected utilization of rebates by benefit plan participants and payor mix of the Company's gross sales.

How We Addressed the Matter in Our Audit We obtained an understanding, evaluated the design, and tested the operating effectiveness of controls over the Company's estimate for Medicare Part D rebates including management's review of the significant assumptions described above and inputs into the rebate calculation. For example, we tested controls over actual sales and the accuracy of forecasting expected utilization and payor mix.

To test the estimate for Medicare Part D rebates, we obtained management's calculation and performed the following audit procedures, among others. We performed a lookback analysis comparing historical Medicare Part D rebate estimates to the amounts invoiced and paid for the same period, performed sensitivity analyses over certain of the subjective assumptions to the calculation to evaluate the impact on the Medicare Part D rebate estimate, performed procedures over the completeness and accuracy of the data used in management's estimates, and tested management's calculation of expected rebate utilization for in-channel inventory.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2015.

San Diego, California
February 28, 2022

ACADIA PHARMACEUTICALS INC.
CONSOLIDATED BALANCE SHEETS
(in thousands, except share and per share amounts)

	December 31,	
	2021	2020
Assets		
Cash and cash equivalents	$ 147,435	$ 326,028
Investment securities, available-for-sale	373,271	305,930
Accounts receivable, net	64,366	48,247
Interest and other receivables	978	2,035
Inventory	7,881	9,682
Prepaid expenses	23,892	25,694
Total current assets	617,823	717,616
Property and equipment, net	8,047	9,161
Operating lease right-of-use assets	58,268	47,283
Intangible assets, net	—	1,108
Restricted cash	5,770	5,770
Long-term inventory	6,217	—
Other assets	3,997	1,678
Total assets	$ 700,122	$ 782,616
Liabilities and stockholders' equity		
Accounts payable	$ 6,876	$ 8,493
Accrued liabilities	89,192	97,474
Total current liabilities	96,068	105,967
Operating lease liabilities	56,126	44,460
Other long-term liabilities	7,034	5,180
Total liabilities	159,228	155,607
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 5,000,000 shares authorized at December 31, 2021 and 2020; no shares issued and outstanding at December 31, 2021 and 2020	—	—
Common stock, $0.0001 par value; 225,000,000 shares authorized at December 31, 2021 and 2020; 161,012,695 shares and 159,637,771 shares issued and outstanding at December 31, 2021 and 2020, respectively	16	16
Additional paid-in capital	2,694,646	2,612,663
Accumulated deficit	(2,153,576)	(1,985,706)
Accumulated other comprehensive (loss) income	(192)	36
Total stockholders' equity	540,894	627,009
Total liabilities and stockholders' equity	$ 700,122	$ 782,616

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

ACADIA PHARMACEUTICALS INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except per share amounts)

	Years Ended December 31,		
	2021	2020	2019
Revenues			
Product sales, net	$ 484,145	$ 441,755	$ 339,076
Total revenues	484,145	441,755	339,076
Operating expenses			
Cost of product sales	10,843	10,211	11,344
License fees and royalties	8,298	10,339	8,254
Research and development	239,415	319,130	240,385
Selling, general and administrative	396,028	388,661	325,638
Total operating expenses	654,584	728,341	585,621
Loss from operations	(170,439)	(286,586)	(246,545)
Interest income, net	591	6,610	11,165
Other income (expense)	2,329	(997)	997
Loss before income taxes	(167,519)	(280,973)	(234,383)
Income tax expense	351	611	876
Net loss	$ (167,870)	$ (281,584)	$ (235,259)
Net loss per common share, basic and diluted	$ (1.05)	$ (1.79)	$ (1.60)
Weighted average common shares outstanding, basic and diluted	160,493	157,331	147,199

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

ACADIA PHARMACEUTICALS INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)

	Years Ended December 31,		
	2021	2020	2019
Net loss	$ (167,870)	$ (281,584)	$ (235,259)
Other comprehensive (loss) income :			
Unrealized (loss) gain on investment securities	(235)	(253)	667
Foreign currency translation adjustments	7	(8)	2
Comprehensive loss	$ (168,098)	$ (281,845)	$ (234,590)

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

ACADIA PHARMACEUTICALS INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Years Ended December 31,		
	2021	2020	2019
Cash flows from operating activities			
Net loss	$ (167,870)	$ (281,584)	$ (235,259)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation	63,615	84,422	82,265
Amortization of premiums and accretion of discounts on investment securities	2,404	1,470	(3,613)
Amortization of intangible assets	1,108	1,477	1,477
(Gain) loss on strategic investment	(2,329)	997	(997)
Depreciation	2,236	1,455	1,289
Loss on disposal of assets	—	281	3
Non-cash in-process research and development	—	44,280	—
Changes in operating assets and liabilities:			
Accounts receivable, net	(16,119)	(12,466)	(9,691)
Interest and other receivables	1,057	58	(394)
Inventory	(4,210)	(3,320)	(1,737)
Prepaid expenses and other current assets	1,802	(7,088)	2,121
Operating lease right-of-use assets	6,287	4,280	3,875
Other assets	10	182	39
Accounts payable	(1,617)	1,271	4,055
Accrued liabilities	(8,455)	27,569	6,458
Operating lease liabilities	(5,433)	(1,769)	(2,518)
Long-term liabilities	1,854	2,319	1,497
Net cash used in operating activities	(125,660)	(136,166)	(151,130)
Cash flows from investing activities			
Purchases of investment securities	(492,797)	(339,908)	(578,634)
Maturities of investment securities	422,817	540,004	413,927
Net purchases of property and equipment	(1,122)	(7,587)	(1,129)
Net cash (used in) provided by investing activities	(71,102)	192,509	(165,836)
Cash flows from financing activities			
Proceeds from issuance of common stock, net of issuance costs	18,162	80,996	371,847
Net cash provided by financing activities	18,162	80,996	371,847
Effect of exchange rate changes on cash	7	(8)	2
Net (decrease) increase in cash, cash equivalents and restricted cash	(178,593)	137,331	54,883
Cash, cash equivalents and restricted cash			
Beginning of year	331,798	194,467	139,584
End of year	$ 153,205	$ 331,798	$ 194,467
Supplemental disclosure of cash flow information:			
Cash paid for income taxes	$ 1,038	$ 1,113	$ 1,597
Supplemental disclosure of noncash information:			
Property and equipment purchases in accounts payable and accrued liabilities	$ —	$ 130	$ 34
Value of common stock issued in connection with asset acquisition	$ —	$ 44,280	$ —

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

ACADIA PHARMACEUTICALS INC.
CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY
(in thousands, except share amounts)

	Common Stock		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
	Shares	Amount				
Balances at December 31, 2018	143,853,597	$ 14	$ 1,948,300	$ (1,468,863)	$ (372)	$ 479,079
Issuance of common stock in public offering, net of issuance costs	7,187,500	1	271,451	—	—	271,452
Issuance of common stock from exercise of stock options and units	3,965,166	—	95,984	—	—	95,984
Issuance of common stock pursuant to employee stock purchase plan	269,037	—	4,411	—	—	4,411
Net loss	—	—	—	(235,259)	—	(235,259)
Stock-based compensation	—	—	82,799	—	—	82,799
Other comprehensive income	—	—	—	—	669	669
Balances at December 31, 2019	155,275,300	15	2,402,945	(1,704,122)	297	699,135
Issuance of common stock in connection with asset acquisition	1,156,626	—	44,280	—	—	44,280
Issuance of common stock from exercise of stock options	2,827,586	1	73,833	—	—	73,834
Issuance of common stock pursuant to employee stock purchase plan	378,259	—	7,162	—	—	7,162
Net loss	—	—	—	(281,584)	—	(281,584)
Stock-based compensation	—	—	84,443	—	—	84,443
Other comprehensive income	—	—	—	—	(261)	(261)
Balances at December 31, 2020	159,637,771	16	2,612,663	(1,985,706)	36	627,009
Issuance of common stock from exercise of stock options and units	1,078,074	—	12,850	—	—	12,850
Issuance of common stock pursuant to employee stock purchase plan	296,850	—	5,312	—	—	5,312
Net loss		—		(167,870)		(167,870)
Stock-based compensation	—	—	63,821	—	—	63,821
Other comprehensive income	—	—			(228)	(228)
Balances at December 31, 2021	161,012,695	$ 16	$ 2,694,646	$ (2,153,576)	$ (192)	$ 540,894

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

ACADIA PHARMACEUTICALS INC.
NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

1. Organization and Business

Acadia Pharmaceuticals Inc. (the Company), based in San Diego, California, is a biopharmaceutical company focused on the development and commercialization of innovative medicines to address unmet medical needs in central nervous system disorders. The Company is incorporated in Delaware.

In April 2016, the U.S. Food and Drug Administration (FDA) approved the Company's first drug, NUPLAZID® (pimavanserin), for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis (PDP). NUPLAZID became available for prescription in the United States on May 31, 2016.

2. Summary of Significant Accounting Policies

Significant accounting policies followed in the preparation of these financial statements are as follows:

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries located in Europe. All intercompany accounts and transactions have been eliminated in consolidation.

Use of Estimates

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

Cash and Cash Equivalents

The Company considers all highly liquid investments with a maturity date at the date of purchase of three months or less to be cash equivalents.

The following table provides a reconciliation of cash, cash equivalents and restricted cash reported in the consolidated balance sheets that sum to the total of the same such amounts shown in the Consolidated Statements of Cash Flows (in thousands).

	Twelve Months Ended December 31, 2021		Twelve Months Ended December 31, 2020	
	Beginning of period	End of period	Beginning of period	End of period
Cash and cash equivalents	$ 326,028	$ 147,435	$ 189,680	$ 326,028
Restricted cash	5,770	5,770	4,787	5,770
Total cash, cash equivalents and restricted cash shown in the statements of cash flows	$ 331,798	$ 153,205	$ 194,467	$ 331,798

Investment Securities

Currently, all of the Company's investment securities are debt securities. The Company has classified all of its investment securities as available-for-sale as the sale of such securities may be required prior to maturity to implement management strategies, and accordingly, carries these investments at fair value. Unrealized gains and losses, if any, are reported as a separate component of stockholders' equity. The cost of investment securities classified as available-for-sale is adjusted for amortization of premiums and accretion of discounts to maturity. Such amortization and accretion are included in interest income. Realized gains and losses, if any, are also included in interest income. The cost of securities sold is based on the specific identification method.

Fair Value of Financial Instruments

The carrying values of the Company's financial instruments, consisting of cash and cash equivalents, trade receivables, interest and other receivables, restricted cash, and accounts payable and accrued liabilities, approximate fair value due to the relative short-term nature of these instruments.

As disclosed in Note 4, the Company classifies its cash equivalents and available-for-sale investment securities within the fair value hierarchy as defined by authoritative guidance:

Level 1 Inputs	—	Quoted prices for identical instruments in active markets.
Level 2 Inputs	—	Quoted prices for similar instruments in active markets; quoted prices for identical or similar instruments in markets that are not active; and model-derived valuations in which all significant inputs and significant value drivers are observable.
Level 3 Inputs	—	Valuation derived from valuation techniques in which one or more significant inputs or significant value drivers are unobservable.

Accounts Receivable

Accounts receivable are recorded net of customer allowances for distribution fees, prompt payment discounts, chargebacks, and credit losses. Allowances for distribution fees, prompt payment discounts and chargebacks are based on contractual terms. The Company adopted FASB Accounting Standards Codification 326-20, *Financial Instruments – Credit Losses* (ASC 326-20) as of January 1, 2020. The Company estimated the current expected credit losses of its accounts receivable by assessing the risk of loss and available relevant information about the 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. Based on its assessment, as of December 31, 2021, the Company determined that an allowance for credit loss was not required.

Although the Company has not historically experienced significant credit losses, the Company's exposure may increase due to uncertainties associated with the global economic recession and other disruptions resulting from the COVID-19 pandemic.

Inventory

Inventory is stated at the lower of cost or net realizable value under the first-in, first-out method (FIFO). The Company uses a combination of standard and actual costing methodologies to determine the cost basis for its inventories which approximates actual costs. Inventory consists of raw material, work in process, and finished goods, including third-party manufacturing costs, freight, and indirect overhead costs. The Company capitalizes inventory costs associated with its products upon regulatory approval when, based on management's judgment, future commercialization is considered probable and the future economic benefit is expected to be realized; otherwise, such costs are expensed. Prior to FDA approval of NUPLAZID in April 2016, all costs related to the manufacturing of NUPLAZID were charged to research and development expense in the period incurred.

The Company periodically reviews inventory and reduces the carrying value of items to net realizable value for potentially excess, dated or obsolete inventory based on an analysis of forecasted demand compared to quantities on hand and any firm purchase orders, as well as product shelf life. During the years ended December 31, 2021, 2020 and 2019, the Company recorded charges of $1.3 million, $0.4 million and $1.1 million, respectively, to reduce certain finished goods and work in process inventory to its net realizable value.

Property and Equipment

Property and equipment are recorded at cost and depreciated over their estimated useful lives using the straight-line method. Leasehold improvements are amortized over the shorter of their estimated useful lives or the term of the lease by use of the straight-line method. Construction-in-process reflects amounts incurred for property, equipment or improvements that have not been placed in service. Maintenance and repair costs are expensed as incurred. When assets are retired or sold, the assets and accumulated depreciation are removed from the respective accounts and any gain or loss is recognized. Estimated useful lives by major asset category are as follows:

	Useful Lives
Machinery and equipment	5 to 7 years
Computers and software	3 years
Furniture and fixtures	10 years

Impairment of Long-Lived Assets

The Company reviews its long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. Recoverability is measured by a comparison of the carrying amount of an asset to estimated undiscounted future cash flows expected to be generated by the asset. If the carrying amount of an asset exceeds its estimated future cash flows, an impairment charge is recognized by the amount by which the carrying amount of the asset exceeds the fair value of the asset. Through December 31, 2021, no such impairment losses have been recorded by the Company.

License Fees and Royalties

The Company expenses amounts paid to acquire licenses associated with products under development when the ultimate recoverability of the amounts paid is uncertain and the technology has no alternative future use when acquired. Acquisitions of technology licenses are charged to expense or capitalized based upon management's assessment regarding the ultimate recoverability of the amounts paid and the potential for alternative future use. The Company has determined that technological feasibility for its product candidates is reached when the requisite regulatory approvals are obtained to make the product available for sale.

In connection with the FDA approval of NUPLAZID in April 2016, the Company made a one-time milestone payment of $8.0 million pursuant to its 2006 license agreement with the Ipsen Group in which the Company licensed certain intellectual property rights that complement its patent portfolio for its serotonin platform, including NUPLAZID. The Company capitalized the $8.0 million payment as an intangible asset and is amortizing the asset on a straight-line basis over the estimated useful life of the licensed patents through the second half of 2021. The Company recorded amortization expense related to its intangible asset of $1.1 million, $1.5 million and $1.5 million for the years ended December 31, 2021, 2020 and 2019. As of December 31, 2021, the intangible asset was fully amortized.

Royalties incurred in connection with the Company's license agreement with the Ipsen Group, as disclosed in Note 9, are expensed to license fees and royalties as revenue from product sales is recognized.

Acquisitions

The Company accounts for acquisitions of an asset or group of similar identifiable assets that do not meet the definition of a business as asset acquisition using the cost accumulation method, whereby the cost of the acquisition, including certain transaction costs, is allocated to the assets acquired on the basis of their relative fair values. No goodwill is recognized in an asset acquisition. Intangible assets acquired in an asset acquisition for use in research and development activities which have no alternative future use are expensed as in-process research and development on the acquisition date. Intangible assets acquired for use in research and development activities which have an alternative future use are capitalized as in-process research and development. Future costs to develop these assets are recorded to research and development expense as they are incurred. Contingent milestone payments associated with asset acquisitions are recognized when probable and estimable. These amounts are expensed to research and development if there is no alternative future use associated with the asset, or capitalized as an intangible asset if alternative future use of the asset exists.

Advertising Expense

In connection with the FDA approval and commercial launch of NUPLAZID in 2016, the Company began to incur advertising costs. Advertising costs are expensed when services are performed or goods are delivered. The Company incurred $41.8 million, $51.1 million and $38.3 million in advertising costs during the years ended December 31, 2021, 2020 and 2019, respectively, related to NUPLAZID. No advertising costs were capitalized as prepaid expenses at December 31, 2021 or 2020.

Revenue Recognition

Product Sales, Net

The Company accounts for contracts with its customers in accordance with *Revenue from Contracts with Customers (Topic 606)*. The Company recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the Company expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that the Company determines are within the scope of Topic 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 Company satisfies a performance obligation. The Company only applies the five-step model to contracts 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 Topic 606, the Company assesses the goods or services promised within each contract, 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. Payment terms differ by customer, but typically range from 31 to 35 days from the date of shipment. Revenue for the Company's product sales has not been adjusted for the effects of a financing component as the Company expects, at contract inception, that the period between when the Company transfers control of the product and when the Company receives payment will be one year or less.

The Company's net product sales consist of U.S. sales of NUPLAZID. NUPLAZID was approved by the FDA in April 2016 and the Company commenced shipments of NUPLAZID to specialty pharmacies (SPs) and specialty distributors (SDs) in late May 2016. SPs dispense product to a patient based on the fulfillment of a prescription and SDs sell product to government facilities, long-term care pharmacies, or in-patient hospital pharmacies. Product shipping and handling costs are included in cost of product sales.

The Company recognizes revenue from product sales at the net sales price (the "transaction price") which includes estimates of variable consideration for which reserves for sales discounts and allowance are established and reflects each of these as either a reduction to the related account receivable or as an accrued liability, depending on how the amount payable is settled. Overall, these reserves reflect the Company's best estimates of the amount of consideration to which the Company is entitled based on the terms of the contract. 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 it is 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 Company's estimates. If actual results in the future vary from estimates, the Company may need to adjust its estimates, which would affect net revenue in the period of adjustment. The following are the Company's significant categories of sales discounts and allowances:

Distribution Fees: Distribution fees include distribution service fees paid to the SPs and SDs based on a contractually fixed percentage of the wholesale acquisition cost (WAC), fees for data, and prompt payment discounts. Distribution fees are recorded as an offset to revenue based on contractual terms at the time revenue from the sale is recognized.

Rebates: Allowances for rebates include mandated discounts under the Medicaid Drug Rebate Program and the Medicare Part D prescription drug benefit. Rebates are amounts owed after the final dispensing of the product to a benefit plan participant and are based upon contractual agreements with, or statutory requirements pertaining to, Medicaid and Medicare benefit providers. The allowance for rebates is based on statutory discount rates, estimated payor mix, and expected utilization. The Company's estimates for expected utilization of rebates are based on historical data received from the SPs and SDs since product launch. Rebates are generally invoiced and paid in arrears so that the accrual balance consists of an estimate of the amount expected to be incurred for the current quarter's activity, plus an accrual balance for prior quarters' unpaid rebates still estimated to be incurred.

Chargebacks: Chargebacks are discounts and fees that relate to contracts with government and other entities purchasing from the SDs at a discounted price. The SDs charge back to the Company the difference between the price initially paid by the SDs and the discounted price paid to the SDs by these entities. The Company also incurs group purchasing organization fees for transactions through certain purchasing organizations. The Company estimates sales with these entities and accrues for anticipated chargebacks and organization fees, based on the applicable contractual terms.

Co-Payment Assistance: The Company offers co-payment assistance to commercially insured patients meeting certain eligibility requirements. Co-payment assistance is accrued for based on actual program participation and estimates of program redemption using data provided by third-party administrators.

Product Returns: Consistent with industry practice, the Company offers the SPs and SDs limited product return rights for damages, shipment errors, and expiring product; provided that the return is within a specified period around the product expiration date as set forth in the applicable individual distribution agreement. The Company does not allow product returns for product that has been dispensed to a patient. As the Company receives inventory reports from the SPs and SDs and has the ability to control the amount of product that is sold to the SPs and SDs, it is able to make a reasonable estimate of future potential product returns based on this on-hand channel inventory data and sell-through data obtained from the SPs and SDs. In arriving at its estimate for product returns, the Company also considers historical product returns, the underlying product demand, and industry data specific to the specialty pharmaceutical distribution industry.

Research and Development Expenses

Research and development expenses are charged to operations as incurred. Research and development expenses include costs associated with services provided by contract organizations for preclinical development, pre-commercialization manufacturing expenses, and clinical trials, salaries and related personnel expenses including stock-based compensation expense, and facilities and equipment expenses. The upfront consideration and transaction costs associated with acquired in-process research and development are also included in the research and development expenses.

The Company accrues for costs incurred as the services are being provided by monitoring the status of the trial or services provided and the invoices received from its external service providers. When the Company makes payments in advance of services being provided, it records those amounts as prepaid expenses on its consolidated balance sheet and expense them as the services are rendered. In the case of clinical trials, a portion of the estimated cost normally relates to the projected cost to treat a patient in the trials, and this cost is recognized based on the number of patients enrolled in the trial. Other indirect costs are generally recognized on a straight-line basis over the estimated period of the study. As actual costs become known, the Company adjusts its accruals accordingly.

Concentration Risk

Financial instruments, which potentially subject the Company to concentrations of credit risk, principally consist of cash, cash equivalents, investment securities, accounts receivable, and restricted cash. The Company invests its excess cash primarily in money market funds, U.S. treasury notes, and high quality, marketable debt instruments of corporations and government sponsored enterprises in accordance with the Company's investment policy. The Company's investment policy defines allowable investments and establishes guidelines relating to credit quality, diversification, and maturities of its investments to preserve principal and maintain liquidity. All investment securities have a credit rating of at least Aa3/AA- or better, or P-1/A-1 or better, as determined by Moody's Investors Service or Standard & Poor's. Further, the Company specifies credit quality standards for its customers that are designed to limit the Company's credit exposure to any single party.

The Company does not currently have any of its own manufacturing facilities, and therefore it depends on an outsourced manufacturing strategy for the production of NUPLAZID for commercial use and for the production of its product candidates for clinical trials. The Company has contracts in place with two third-party manufacturers of commercial drug product and one third-party manufacturer of drug substance that is approved for the production of NUPLAZID active pharmaceutical ingredient (API). Although there are potential sources of supply other than the Company's existing suppliers, any new supplier would be required to qualify under applicable regulatory requirements.

The Company has entered into distribution agreements with a limited number of SPs and SDs, and all of the Company's product sales are to these customers. For the year ended December 31, 2021, the Company's four largest customers represented approximately 74% of the Company's product revenue and 77% of the Company's accounts receivable balance at December 31, 2021. For the year ended December 31, 2020, the Company's four largest customers represented approximately 74% of the Company's product revenue and 75% of the Company's accounts receivable balance at December 31, 2020. For the year ended December 31, 2019, the Company's four largest customers represented approximately 77% of the Company's product revenue and 75% of the Company's accounts receivable balance at December 31, 2019.

Stock-Based Compensation

The fair value of each employee stock option and each employee stock purchase right granted is estimated on the grant date under the fair value method using the Black-Scholes valuation model. The estimated fair value of each stock option and purchase right is then expensed over the requisite service period, which is generally the vesting period. The following weighted-average assumptions were used during these periods:

	Years Ended December 31,		
	2021	2020	2019
Stock Options:			
Expected volatility	64 %	63 %	62 %
Risk-free interest rate	1 %	1 %	2 %
Expected dividend yield	0 %	0 %	0 %
Expected life of options in years	5.4	5.5	5.7

	Years Ended December 31,		
	2021	2020	2019
Employee Stock Purchase Plan:			
Expected volatility	49%-100%	50%-76%	62%-86%
Risk-free interest rate	0.0%-0.5%	0.1%-0.2%	1.5%-2.4%
Expected dividend yield	0 %	0 %	0 %
Expected life in years	0.5-2.0	0.5-2.0	0.5-2.0

Expected Volatility. The Company considers its historical volatility and implied volatility when determining the expected volatility.

Risk-Free Interest Rate. The Company determines its risk-free interest rate assumption based on the U.S. Treasury yield for obligations with contractual terms similar to the expected term of the stock option or purchase right being valued.

Expected Dividend Yield. The Company has never paid any dividends and currently has no plans to do so.

Expected Life. In determining the expected life for stock options, the Company considers, among other factors, its historical exercise experience to date as well as the mean time remaining to full vesting of all outstanding options and the mean time remaining to the end of the contractual term of all outstanding options. The estimated life for the Company's employee stock purchase rights is based upon the terms of each offering period.

The fair value of restricted stock units (RSUs) is estimated based on the closing market price of the Company's common stock on the date of grant. RSUs generally vest over a four-year period. Certain RSUs also have an accelerated vesting clause based on specified market condition target and continued employment through a minimum vesting period. The fair value of RSUs expected to vest are recognized and amortized on a straight-line basis over the requisite service period, which is generally the vesting period. For those RSUs requiring satisfaction of both market and service conditions, the requisite service period is the longest of the explicit, implicit and derived service periods. The fair value of performance-based stock units (PSUs) is estimated based on the closing market price of the Company's common stock on the date of grant. PSUs vest upon the achievement of certain pre-defined company-specific performance-based criteria. Expense related to these PSUs is recognized ratably over the expected performance period once the pre-defined performance-based criteria for vesting becomes probable. During the year ended December 31, 2021, the Company had a change in estimate related to the achievement of certain performance-based criteria for performance-based stock awards which resulted in a reduction in stock-based compensation expenses by approximately $6.8 million.

The table below summarizes the total stock-based compensation expense included in the Company's statements of operations for the periods presented (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Cost of product sales	$ 1,286	$ 2,632	$ 2,936
Research and development	21,969	31,314	32,533
Sales, general and administrative	40,360	50,476	46,796
	$ 63,615	$ 84,422	$ 82,265

Income Taxes

Current income tax expense or benefit represents the amount of income taxes expected to be payable or refundable for the current year. A deferred income tax asset or liability is computed for the expected future impact of differences between the financial reporting and income tax bases of assets and liabilities and for the expected future tax benefit to be derived from tax credits and loss carryforwards. Deferred income tax expense or benefit represents the net change during the year in the deferred income tax asset or liability. Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized.

The Company recognizes the impact of a tax position in the financial statements only if that position is more likely than not to be sustained upon examination by taxing authorities, based on the technical merits of the position. Any interest and penalties related to uncertain tax positions will be reflected in income tax expense.

Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss by the weighted average number of common shares outstanding for the period, without consideration for common stock equivalents. Diluted net loss per share is computed by dividing the net loss by the weighted average number of common shares and common stock equivalents outstanding for the period determined using the treasury stock method. For purposes of this calculation, stock options, employee stock purchase rights, RSUs, and warrants are considered to be common stock equivalents but are not included in the calculations of diluted net loss per share for the periods presented as their effect would be antidilutive. The Company incurred net losses for all periods presented and there were no reconciling items for potentially dilutive securities. More specifically, at December 31, 2021, 2020 and 2019, options, employee stock purchase rights, RSUs, PSUs, and warrants covering a total of approximately 17,535,000 shares, 19,331,000 shares and 19,516,000 shares, respectively, were excluded from the calculation of diluted net loss per share as their effect would have been anti-dilutive.

Segment Reporting

Management has determined that the Company operates in one business segment which is the development and commercialization of innovative medicines. All revenues for the years ended December 31, 2021, 2020 and 2019 were generated from customers in the United States.

Recently Issued Accounting Standards

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments-Credit Losses: Measurement of Credit Losses on Financial Instruments*, which changes the impairment model for most financial assets and certain other instruments. For trade receivables and other instruments, entities will be required to use a new forward-looking expected loss model that generally will result in the earlier recognition of allowances for losses. For available-for-sale debt securities with unrealized losses, the losses will be recognized as allowances rather than as reductions in the amortized cost of the securities. This guidance is effective for annual reporting periods beginning after December 15, 2019, including interim periods within those years, with early adoption permitted only as of annual reporting periods beginning after December 15, 2018. The Company adopted this guidance on January 1, 2020. The adoption of ASU 2016-13 did not have material impact on the Company's consolidated financial statements.

In April 2019, the FASB issued ASU 2019-04, *Codification Improvements to Topic 326, Financial Instruments—Credit Losses, Topic 815, Derivatives and Hedging, and Topic 825, Financial Instruments*, which, among other things, provides entities with practical expedients and policy elections related to the presentation and disclosure of accrued interest and the related allowance for credit losses and clarifies how to disclose line-of-credit arrangements that are converted to term loans in the vintage table disclosure. ASU 2019-04 has the same effective date as the new credit impairment standard for entities that have not yet adopted the standard. For entities that early adopted the new credit impairment standard, ASU 2019-04 is effective for fiscal years beginning after December 15, 2019 and interim periods therein. Entities that early adopted the new credit impairment standard may early adopt ASU 2019-04. The Company adopted this guidance on January 1, 2020. There was no significant impact of the adoption of this guidance on the Company's consolidated financial statements.

In December 2019, the FASB issued ASU 2019-12 Income Taxes (Topic 740), *Simplifying the Accounting for Income Taxes*. The Board issued this Update as part of its Simplification Initiative to improve areas of GAAP and reduce cost and complexity while maintaining usefulness. The main provision that impacts the Company is the removal of the exception to the incremental approach of intra-period tax allocation when there is a loss from continuing operations and income or gain from other items (for example, discontinued operations and other comprehensive income). ASU 2019-12 is effective for annual periods, and interim periods within those annual periods, beginning after December 15, 2020. Early adoption is permitted, including adoption in an interim period. The Company has elected to early adopt ASU 2019-12 as of the beginning of 2020, however, there is no cumulative effect to be recognized with the early adoption and no material impact on the Company's consolidated financial statements.

3. Investments

The carrying value and amortized cost of the Company's investments, summarized by major security type, consisted of the following (in thousands):

	December 31, 2021			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
U.S. Treasury notes	$ 140,287	$ —	$ (100)	$ 140,187
Government sponsored enterprise securities	49,512	—	(38)	49,474
Municipal bonds	26,006	—	(22)	25,984
Commercial paper	157,670	9	(53)	157,626
	$ 373,475	$ 9	$ (213)	$ 373,271

	December 31, 2020			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
U.S. Treasury notes	$ 205,111	$ 6	$ (27)	$ 205,090
Government sponsored enterprise securities	10,004	—	(5)	9,999
Corporate debt securities	52,341	47	— *	52,388
Commercial paper	38,443	21	(11)	38,453
	$ 305,899	$ 74	$ (43)	$ 305,930

* Unrealized loss was less than $500.

The Company has classified all of its available-for-sale investment securities, including those with maturities beyond one year, as current assets on its consolidated balance sheets based on the highly liquid nature of the investment securities and because these investment securities are considered available for use in current operations. As of December 31, 2021 and 2020, all of the Company's available-for-sale investment securities have contractual maturity dates of less than one year. The Company has classified all equity securities as other assets on its consolidated balance sheets.

At December 31, 2021 and 2020, the Company had 39 and 24 securities, respectively, in an unrealized loss position. The following table presents gross unrealized losses and fair value for those available-for-sale investments that were in an unrealized loss position as of December 31, 2021 and December 31, 2020, aggregated by investment category and length of time that individual securities have been in a continuous loss position (in thousands):

	Less Than 12 Months		12 Months or Greater		Total	
	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses
December 31, 2021:						
U.S. Treasury notes	$ 140,287	$ (100)	$ —	$ —	$ 140,287	$ (100)
Government sponsored enterprise securities	49,512	(38)	—	—	49,512	(38)
Municipal bonds	26,006	(22)	—	—	26,006	(22)
Commercial paper	75,192	(53)	—	—	75,192	(53)
Total	$ 290,997	$ (213)	$ —	$ —	$ 290,997	$ (213)
December 31, 2020:						
U.S. Treasury notes	$ 129,631	$ (27)	$ —	$ —	$ 129,631	$ (27)
Government sponsored enterprise securities	10,004	(5)	—	—	10,004	(5)
Corporate debt securities	6,252	— *	—	—	6,252	— *
Commercial paper	23,466	(11)	—	—	23,466	(11)
Total	$ 169,353	$ (43)	$ —	$ —	$ 169,353	$ (43)

* Unrealized loss was less than $500.

At each reporting date, the Company performs an evaluation of impairment to determine if any unrealized losses are the result of credit losses. Impairment is assessed at the individual security level. Factors considered in determining whether a loss resulted from a credit loss or other factors include the Company's intent and ability to hold the investment until the recovery of its amortized cost basis, the extent to which the fair value is less than the amortized cost basis, the length of time and extent to which fair value has been less than the cost basis, the financial condition of the issuer, any historical failure of the issuer to make scheduled interest or principal payments, any changes to the rating of the security by a rating agency, any adverse legal or regulatory events affecting the issuer or issuer's industry, any significant deterioration in economic conditions.

The Company does not intend to sell the investment in unrealized loss position and it is unlikely that the Company will be required to sell the investment before the recovery of its amortized cost basis. Based on its evaluation, the Company determined its year-to-date credit losses related to its available-for-sale securities were immaterial at December 31, 2021.

Although the Company has not historically experienced significant losses on its investments, the Company's exposure may increase due to uncertainties associated with the global economic recession and other disruptions resulting from the COVID-19 pandemic.

4. Fair Value Measurements

The Company's investments include cash equivalents, available-for-sale investment securities consisting of money market funds, U.S. treasury notes, and marketable debt instruments of corporations and government sponsored enterprises in accordance with the Company's investment policy, and equity investments. The Company's investment policy defines allowable investment securities and establishes guidelines relating to credit quality, diversification, and maturities of its investments to preserve principal and maintain liquidity. All investment securities have a credit rating of at least Aa3/AA- or better, or P-1/A-1 or better, as determined by Moody's Investors Service or Standard & Poor's.

The Company's cash equivalents, available-for-sale investment securities, and equity securities are classified within the fair value hierarchy as defined by authoritative guidance. The Company's investment securities and equity securities classified as Level 1 are valued using quoted market prices. The Company obtains the fair value of its Level 2 financial instruments from third-party pricing services. The pricing services utilize industry standard valuation models whereby all significant inputs, including benchmark yields, reported trades, broker/dealer quotes, issuer spreads, bids, offers, or other market-related data, are observable. The Company validates the prices provided by the third-party pricing services by reviewing their pricing methods and matrices and obtaining market values from other pricing sources. After completing the validation procedures, the Company did not adjust or override any fair value measurements provided by these pricing services as of December 31, 2021 and 2020, respectively.

The Company does not hold any securities classified as Level 3, which are securities valued using unobservable inputs. The Company has not transferred any investment securities between the classification levels.

The recurring fair value measurements of the Company's cash equivalents, available-for-sale investment securities, and equity securities at December 31, 2021 and 2020 consisted of the following (in thousands):

		Fair Value Measurements at Reporting Date Using		
	December 31, 2021	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Money market fund	$ 122,876	$ 122,876	$ —	$ —
U.S. Treasury notes	140,187	140,187	—	—
Equity securities	3,638	3,638	—	—
Government sponsored enterprise securities	49,474	—	49,474	—
Municipal bonds	25,984	—	25,984	—
Commercial paper	157,626	—	157,626	—
	$ 499,785	$ 266,701	$ 233,084	$ —

		Fair Value Measurements at Reporting Date Using		
	December 31, 2020	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Money market fund	$ 300,339	$ 300,339	$ —	$ —
U.S. Treasury notes	230,088	230,088	—	—
Equity securities	1,309	1,309	—	—
Government sponsored enterprise securities	9,999	—	9,999	—
Corporate debt securities	52,388	—	52,388	—
Commercial paper	38,453	—	38,453	—
	$ 632,576	$ 531,736	$ 100,840	$ —

5. Balance Sheet Details

Inventory consisted of the following (in thousands):

	December 31,	
	2021	2020
Finished goods	$ 1,114	$ 1,453
Work in process	6,767	6,367
Raw material	6,217	1,862
	$ 14,098	$ 9,682
Reported as:		
Inventory	$ 7,881	$ 9,682
Long-term inventory	6,217	—
Total	$ 14,098	$ 9,682

Amount reported as long-term inventory consisted of raw materials as of December 31, 2021. The Company has raw materials beyond one year production plan that prevent the Company from potential supply interruption. Those raw materials that beyond one year production plan were classified as long-term inventory.

Property and equipment, net, consisted of the following (in thousands):

	December 31,	
	2021	2020
Computers and software	$ 5,873	$ 5,315
Leasehold improvements	3,696	4,033
Furniture and fixtures	4,549	3,648
Machinery and equipment	113	113
	14,231	13,109
Accumulated depreciation	(6,184)	(3,948)
	$ 8,047	$ 9,161

Depreciation of property and equipment was $2.2 million, $1.5 million, and $1.3 million for the years ended December 31, 2021, 2020, and 2019, respectively. For the year ended December 31, 2021, the Company did not retire any fully depreciated property and equipment. During 2020 and 2019, the Company retired $3.1 million and $0.2 million, respectively, of fully depreciated property and equipment.

Accrued liabilities consisted of the following (in thousands):

	December 31,	
	2021	2020
Accrued research and development services	$ 27,270	$ 28,380
Accrued compensation and benefits	25,896	25,811
Accrued sales allowances	15,717	14,115
Accrued consulting and professional fees	9,319	18,969
Current portion of lease liabilities	8,304	5,087
Other	2,686	5,112
	$ 89,192	$ 97,474

6. Stockholders' Equity

Stock Offerings

In August 2020, the Company entered into an Agreement and Plan of Merger (the Merger Agreement) with CerSci Therapeutics Incorporated (CerSci), pursuant to which one of the Company's wholly owned subsidiaries merged with and into CerSci, with CerSci as the surviving corporation and the Company's wholly owned subsidiary. Approximately 1.2 million shares of the Company's common stock with a value of $44.3 million were issued to CerSci's former equity holders. The Company filed a registration statement on Form S-3 with the SEC to register the resale of the shares of the Company's common stock issued in connection with its acquisition of CerSci.

In September 2019, the Company raised net proceeds of approximately $271.5 million from the sale of 7,187,500 shares of its common stock in a follow-on public offering, including 937,500 shares sold pursuant to the exercise in full of the underwriters' option to purchase additional shares.

Equity Awards

The Company's 2010 Equity Incentive Plan, as amended to date (the 2010 Plan), permits the grant of options to employees, directors and consultants. In addition, the 2010 Plan permits the grant of stock bonuses, rights to purchase restricted stock, and other stock awards. The exercise price of options granted under the 2010 Plan cannot be less than 100 percent of the fair market value of the common stock on the date of grant and the maximum term of any option is 10 years. Options granted under the 2010 Plan generally vest over a four-year period. All shares that remained eligible for grant under the Company's 2004 Equity Incentive Plan (the 2004 Plan) at the time of approval of the 2010 Plan were transferred to the 2010 Plan. The 2010 Plan share reserve also has been, and may be, increased by the number of shares that otherwise would have reverted to the 2004 Plan reserve after June 2010. In June 2015, June 2016, June 2017, June 2018, and June 2019, the Company's stockholders approved amendments to its 2010 Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under the plan by 5,000,000 shares, 3,000,000 shares, 5,500,000 shares, 6,700,000 shares, and 8,300,000 shares, respectively. At December 31, 2021, there were 27,357,064 shares of common stock authorized for issuance, of which 9,590,133 shares were available for new grants under the 2010 Plan.

Stock Options

The 2010 Plan provided for the grant of options to employees, directors and consultants. The exercise price of options granted under the 2010 Plan was at 100 percent of the fair market value of the common stock on the date of grant and the maximum term of any option was 10 years. Options granted under the 2010 Plan generally vested over a four-year period.

The following table summarizes the Company's stock option activity during the year ended December 31, 2021:

	Number of Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2020	16,441,994	$ 30.40		
Granted	1,879,092	$ 43.62		
Exercised	(577,627)	$ 22.25		
Cancelled/forfeited	(2,657,318)	$ 34.83		
Outstanding at December 31, 2021	15,086,141	$ 31.58	5.8	$ 16,416
Vested and exercisable at December 31, 2021	11,003,784	$ 30.09	5.1	$ 12,879
Unvested at December 31, 2021	4,082,357	$ 35.60	7.7	$ 3,537

The aggregate intrinsic value of options exercisable as of December 31, 2021 is calculated as the difference between the exercise price of the underlying options and the closing market price of the Company's common stock on that date, which was $23.34 per share. The aggregate intrinsic value of options exercised during the years ended December 31, 2021, 2020, and 2019 was approximately $8.0 million, $55.5 million, and $56.6 million, respectively, determined as of the date of exercise. The Company received $12.9 million and $73.8 million in cash from options exercised during the year ended December 31, 2021 and 2020, respectively.

The weighted average per share fair value of options granted during the years ended December 31, 2021, 2020, and 2019 was approximately $24.07, $24.16, and $15.97, respectively. As of December 31, 2021 and 2020, total unrecognized compensation cost related to stock options was approximately $66.0 million and $99.1 million, and the weighted average period over which this cost is expected to be recognized is approximately 2.3 years and 2.5 years, respectively.

Restricted Stock

The Company grants RSUs and PSUs, both of which are considered restricted stock, pursuant to the 2010 Plan and satisfies such grants through the issuance of new shares. RSUs are share awards that, upon vesting, will deliver to the holder shares of the Company's common stock. RSUs generally vest over a four-year period. Certain RSUs also has accelerated vesting clause based on specified market condition target and continued employment through the vesting period. PSUs for which the number of shares issuable at the end of performance period can reach up to 200% of the shares approved in the award based on the achievement of certain pre-defined Acadia-specific performance criteria and continued employment through the vesting period.

The following table summarizes the Company's restricted stock activity during the year ended December 31, 2021:

	Number of Shares	Weighted Average Grant Date Fair Value	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2020	2,207,247	$ 33.81	
Granted	1,713,829	$ 35.84	
Vested	(491,813)	$ 30.10	
Cancelled/forfeited	(748,473)	$ 38.74	
Outstanding at December 31, 2021	2,680,790	$ 34.41	$ 62,570

There were 1,276,936 and 700,156 PSUs outstanding at December 31, 2021 and 2020, respectively. During the years ended 2021 and 2020, 918,434 and 255,878 PSUs were granted, respectively, none of which were vested. During the years ended December 31, 2021 and 2020, total intrinsic value of PSUs outstanding was $29.8 million and $37.4 million, respectively. Total unrecognized compensation cost related to RSUs was approximately $39.8 million and $41.7 million for the years ended December 31, 2021 and 2020, respectively, and the weighted average period over which the cost is expected to be recognized is approximately 2.3 years and 2.7 years, respectively. Total unrecognized compensation cost related to PSUs was approximately $11.5 million and $2.6 million for the years ended December 31, 2021 and 2020, respectively, and the weighted average remaining contractual term related to outstanding PSUs was 3.3 years and 2.8 years, respectively.

Employee Stock Purchase Plan

The Company's 2004 Employee Stock Purchase Plan (the Purchase Plan) became effective upon the closing of the Company's initial public offering in June 2004. In June 2016, June 2019 and June 2020, the Company's stockholders approved an amendment to the Purchase Plan to, among other things, increase the aggregate number of shares of common stock authorized for issuance under the plan by 400,000 shares, 600,000 shares and 3,000,000 shares, respectively. At December 31, 2021, a total of 5,525,000 shares of common stock had been reserved for issuance under the Purchase Plan. At December 31, 2021, 2,810,145 shares of common stock remained available for issuance pursuant to the Purchase Plan. Eligible employees who elect to participate in an offering under the Purchase Plan may have up to 15 percent of their earnings withheld, subject to certain limitations, to purchase shares of common stock pursuant to the Purchase Plan. The price of common stock purchased under the Purchase Plan is equal to 85 percent of the lower of the fair market value of the common stock at the commencement date of each offering period or the relevant purchase date.

During the years ended December 31, 2021, 2020, and 2019, a total of 296,850, 377,963, and 269,037 shares of common stock were issued under the Purchase Plan at average per share prices of $17.89, $18.94, and $16.41, respectively. The weighted average per share fair value of purchase rights granted during the years ended December 31, 2021, 2020, and 2019 was $23.97, $22.47, and $14.24, respectively. During the years ended December 31, 2021, 2020, and 2019, the Company recorded cash received from the exercise of purchase rights of $5.3 million, $7.2 million, and $4.4 million, respectively.

Contingent Cash Awards

In November 2021, the Company established a plan whereby substantially all full-time employees excluding executive management are eligible to receive a series of cash bonuses over certain periods based on continued employment and the Company's stock price reaching a pre-specified target. The maximum potential payout of the cash awards at the grant date was $15.1 million. The Company has determined that the cash awards were classified as liabilities pursuant to ASC Topic 718, *Compensation – Stock Compensation*. The Company estimates the fair value of the awards at each reporting period using the Monte Carlo simulation, which is recognized as compensation cost over the derived service period. Total fair value of the awards at the grant date was $4.4 million. The maximum potential payout at December 31, 2021 after adjusting for forfeitures was $14.6 million. The fair value of the awards at December 31, 2021 was approximately $5.6 million. During year ended December 31, 2021, the Company recorded a total of $0.6 million compensation cost related to the awards.

7. 401(k) Plan

Effective January 1997, the Company established a deferred compensation plan (the 401(k) Plan) pursuant to Section 401(k) of the Internal Revenue Code of 1986, as amended (the Code), whereby substantially all employees are eligible to contribute up to 60 percent of their pretax earnings, not to exceed amounts allowed under the Code. The Company makes discretionary contributions to the 401(k) Plan equal to 100 percent of each employee's pretax contributions up to 5 percent of his or her eligible compensation, subject to limitations under the Code. The Company's total contributions to the 401(k) Plan were $5.8 million, $5.1 million, and $4.3 million for the years ended December 31, 2021, 2020, and 2019, respectively.

8. Income Taxes

Domestic and foreign pre-tax loss is as follows (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Domestic	$ (138,913)	$ (238,885)	$ (123,411)
Foreign	(28,606)	(42,088)	(110,972)
	$ (167,519)	$ (280,973)	$ (234,383)

At December 31, 2021, the Company had federal, state, and foreign net operating loss (NOL) carryforwards of approximately $551.2 million, $426.2 million, and $1,354.3 million, respectively. The Company recognized state income tax provisions of $0.4 million, $0.4 million and $0.9 million for the years ended December 31, 2021, 2020 and 2019, respectively. The Company recognized foreign income tax in the amount of $0.2 million for the year ended December 31, 2020. These tax liabilities were associated with minimum taxes and a patent box entry tax for Switzerland. Utilization of the domestic NOL and research and development (R&D) credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that have occurred or that could occur in the future, as required by Section 382 of the Code, as well as similar state and foreign provisions. These ownership changes may limit the amount of NOL and R&D credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an "ownership change" as defined by Section 382 of the Code results from a transaction or series of transactions over a three-year period resulting in an ownership change of more than 50 percentage points of the outstanding stock of a company by certain stockholders or public groups.

The Company previously completed a study to assess whether an ownership change, as defined by Section 382 of the Code, had occurred from the Company's formation through December 31, 2013. Based upon this study, the Company determined that several ownership changes had occurred. Accordingly, the Company reduced its deferred tax assets related to the federal NOL carryforwards and the federal R&D credit carryforwards that are anticipated to expire unused as a result of these ownership changes. These tax attributes were excluded from deferred tax assets with a corresponding reduction of the valuation allowance with no net effect on income tax expense or the effective tax rate. The Company completed a study through December 31, 2020 and concluded no additional ownership changes occurred. Future ownership changes may further limit the Company's ability to utilize its remaining tax attributes.

Federal and state NOL carryforwards of $6.9 million and less than $0.1 million will expire in 2025 unless utilized. The remaining federal and state NOL carryforwards will begin to expire in 2026. At December 31, 2021, the Company had federal and state charitable contribution carryforwards of $171.3 million and $21.8 million will expire in 2022 unless utilized. At December 31, 2021, the Company had $65.8 million of federal R&D credit carryforwards, of which $0.3 million will expire in 2022 unless utilized, and the remaining federal R&D credit carryforwards will begin to expire in 2023. At December 31, 2021, the Company had state R&D credit carryforwards of approximately $2.8 million that will begin to expire in 2024 and $18.5 million that have no expiration date. At December 31, 2021, the Company had foreign NOL carryforwards of approximately $218.5 million that will expire in 2022 unless utilized and $3.4 million that have no expiration date. The Company continues to record the deferred tax assets related to these attributes, subject to valuation allowance, until expiration occurs.

The components of the deferred tax assets are as follows (in thousands):

	December 31,	
	2021	2020
Deferred tax assets		
NOL carryforwards	$ 229,476	$ 218,905
R&D credit carryforwards	74,702	63,886
Stock-based compensation	51,170	47,547
Charitable contributions	41,355	28,470
Lease liabilities	15,550	11,675
Intangibles	6,741	7,109
Capitalized R&D	—	6,073
Other	11,700	9,390
Total deferred tax assets	430,694	393,055
Valuation allowance	(416,630)	(380,533)
Deferred tax liabilities		
Right-of-use assets	(14,063)	(11,142)
Property and equipment	(1)	(1,380)
Total deferred tax liabilities	(14,064)	(12,522)
Total net deferred tax assets	$ —	$ —

Realization of deferred tax assets is dependent upon future earnings, if any, the timing and amount of which are uncertain. Accordingly, the deferred tax assets have been fully offset by a valuation allowance. The valuation allowance increased by approximately $36.1 million in 2021 primarily due to an increase in deferred tax assets generated from net operating losses, R&D credits and stock-based compensation expense, offset in part by the remeasurement of deferred tax balance for changes in state tax rates, and limitations on executive stock compensation.

During 2019, Switzerland implemented tax reform that is effective for tax years 2020 and forward. As a result, the Company has remeasured the deferred tax assets, primarily comprised of net operating loss carryforwards, at the amount and rate in which it is anticipated they will reverse. The tax reform also allowed the Company to take as a deduction for Cantonal purposes only, a portion of the increase in value of the intellectual property transferred to Switzerland. This deduction was available as a result of establishing Lucerne as the Cantonal location for the Company. As a result, during 2019 a deferred tax asset of $57.0 million was established which was the estimated amount that would be allowed as a future deduction. During December 2020, the Company moved to Basel-City from Lucerne. As a result, the intellectual property deduction is no longer available and has been reversed. The deferred tax assets and net operating losses were remeasured at the amount and rate in which they are anticipated to reverse as a result of the change in jurisdiction. The adjustments made to the deferred tax assets are offset by a valuation allowance.

A reconciliation of income taxes to the amount computed by applying the statutory federal income tax rate to the pretax loss is summarized as follows (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Amounts computed at statutory federal rate	$ (35,179)	$ (59,004)	$ (49,365)
Stock-based compensation and other permanent differences	6,696	991	5,691
Write-off of IP R&D	1,277	9,565	—
R&D credits	(11,727)	(17,909)	(16,687)
Change in valuation allowance	36,099	5,925	99,846
State taxes	(2,617)	(5,038)	(2,138)
Contingencies	3,879	2,665	1,861
Foreign rate differential	2,857	4,208	20,413
Limitation on executive compensation	1,808	3,705	1,178
Deferred rate adjustment	(2,424)	2,130	—
Switzerland tax reform	(923)	53,045	(59,181)
Other	605	328	(742)
Income tax expense	$ 351	$ 611	$ 876

The tax years 2002-2020 remain open to examination by the major taxing jurisdictions to which the Company is subject.

The Company recognizes a tax benefit from an uncertain tax position when it is more likely than not that the position will be sustained upon examination. The Company recorded an uncertain tax position reserve of $4.1 million, $2.9 million and $1.9 million for the years ended December 31, 2021, 2020 and 2019, respectively. Due to the valuation allowance recorded against the Company's deferred tax assets, an immaterial amount of the total unrecognized tax benefits as of December 31, 2021 would reduce the annual effective tax rate if recognized. The Company does not anticipate that the amount of unrecognized tax benefits as of December 31, 2021 will significantly change within the next twelve months. The Company's practice is to recognize interest and/or penalties related to uncertain income tax positions in income tax expense. The Company had no interest and/or penalties accrued on the Company's consolidated balance sheets at December 31, 2021 or 2020, respectively. Further, the Company did not recognize any interest and/or penalties in the statement of operations for the years ended December 31, 2021, 2020 and 2019, respectively, related to uncertain tax positions.

The following table provides a reconciliation of changes in unrecognized tax benefits (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Balance at beginning of period	$ 9,843	$ 6,945	$ 5,037
Additions related to current period tax positions	3,973	2,722	1,908
Additions related to prior period tax positions	140	212	—
Reductions related to prior period tax positions	(33)	(36)	—
Balance at end of period	$ 13,923	$ 9,843	$ 6,945

9. Commitments and Contingencies

Royalty Payments

Pursuant to the terms of its 2006 license agreement with the Ipsen Group, the Company is required to make royalty payments of 2% of net sales of NUPLAZID. This obligation terminated in October 2021.

License and Merger Agreements

The Company has entered into various collaboration, licensing and merger agreements which provide the Company with rights to certain know-how, technology and patent rights. The agreements generally include upfront license fees, development and commercial milestone payments upon achievement of certain clinical and commercial development and annual net sales milestones, as well as royalties calculated as a percentage of product revenues, with rates that vary by agreement. The Company incurred $11.0 million, $72.7 million and $1.4 million in upfront and license payments in the years ended December 31, 2021, 2020 and 2019, respectively. These upfront and license payments were included in the research and development expenses in the consolidated statements of operations as there was no alternative future use associated with the payments. As of December 31, 2021, the Company may be required to make milestone payments up to $2.2 billion in the aggregate, of which, $10.0 million may be paid in the next 12 months if the FDA accepts for review of the NDA for trofinetide for the treatment of Rett syndrome.

In May 2018, the Company signed an Exclusivity Deed (the Deed) with Neuren that provided for exclusive negotiations for a period of three months from the date of the Deed. Under the terms of the Deed, the Company invested $3.1 million to subscribe for 1,330,000 shares of Neuren and paid $0.9 million for the exclusive right to negotiate a deal with Neuren, which was recorded in selling, general and administrative expenses in the consolidated statements of operations in the second quarter of 2018. At December 31, 2021, the Company continues to hold the equity securities as a strategic investment in which the Company does not have a controlling interest or significant influence. Publicly held equity securities are measured using quoted prices in their respective active markets with changes recorded through other expense on the statements of operations. Net gain on the strategic investments recognized in other income in the consolidated statements of operations for the year ended December 31, 2021 was $2.3 million, net loss on strategic investments recognized for the year ended December 31, 2020 was $1.0 million and net gain on strategic investments recognized for the year ended December 31, 2019 was $1.0 million. As of December 31, 2021 and 2020, the aggregate carrying amount of the Company's strategic equity investment was $3.6 million and $1.3 million, respectively, included in other assets on the consolidated balance sheets.

In August 2018, the Company entered into a license agreement with Neuren and obtained exclusive North American rights to develop and commercialize trofinetide for Rett syndrome and other indications. Under the terms of the agreement, Neuren received an upfront payment of $10.0 million and is eligible to receive milestone payments of up to $455.0 million, based on the achievement of certain development and annual net sales milestones, including a $10.0 million payment upon the FDA's acceptance of an NDA filing for trofinetide and a $40.0 million payment upon the Company's first commercial sale of trofinetide in North America. In addition, Neuren is eligible to receive tiered, escalating, double-digit percentage royalties based on net sales. The license agreement was accounted for as an asset acquisition and the upfront cash payment of $10.0 million was recorded in research and development expenses in the consolidated statements of operations in the third quarter of 2018, as there is no alternative use for the asset.

Under the license agreement, Neuren and its non-Acadia licensees and sublicensees are prohibited from developing or commercializing any other product (including Neuren's other existing compounds) for Rett syndrome, or for any other indication being developed pursuant to the agreement, in North America. Furthermore, with respect to Neuren's development or commercial activities outside North America, (i) if Neuren is developing trofinetide for the same indication as the Company, Neuren is obligated to use commercially reasonable efforts to conduct such activities in a manner that minimizes any adverse impact on trofinetide in North America, and (ii) if Neuren is developing trofinetide for a different indication, Neuren may not undertake such activities if the Company believes, and the joint steering committee determines, they would be reasonably likely to materially adversely affect the development and commercialization of trofinetide in North America.

In March 2020, the Company entered into a license agreement and research collaboration with Vanderbilt University and obtained exclusive worldwide rights to develop and commercialize novel drug candidates targeting positive allosteric modulators of the muscarinic M1 receptor (the M1 PAM program) with the potential to treat a range of central nervous system disorders. Under the terms of the agreement, the Company paid Vanderbilt University an upfront license fee of $10.0 million and may be required to pay up to $515.0 million in milestone payments based on the achievement of certain clinical and commercial development and annual net sales milestones. In addition, the Company may be required to pay Vanderbilt University tiered royalties based on net sales. Furthermore, the Company is required to spend a minimum annual amount in development and the pursuit of regulatory approval for the M1 PAM compounds over the first three years of the license agreement. Such amounts are not material to the Company. The license agreement was accounted for as an asset acquisition and the upfront cash payment of $10.0 million was expensed to research and development in the first quarter of 2020 as there is no future alternative use for the assets.

In August 2020, the Company entered into the Merger Agreement with CerSci, with CerSci remaining as the surviving corporation and the Company's wholly owned subsidiary. CerSci's lead development program is a unique Reactive Species Decomposition Accelerant, a non-opioid, mechanism focused on interrupting pathways that sensitize neurons to pain. The portfolio contains additional preclinical stage programs, including brain penetrant compounds, with potential for symptomatic and disease modifying treatment utility in neurodegenerative diseases. The Company incurred an aggregate of $52.8 million in upfront consideration and transaction costs, of which, $44.3 million was paid through the issuance of approximately 1.2 million shares of the Company's common stock. In addition, under the terms of the Merger Agreement, the Company may be required to pay CerSci's former equity holders up to $887.0 million in cash upon the achievement of certain development, commercialization and sales milestones, in addition to tiered cash royalties in the mid-single digits based on annual net sales. As substantially all of the fair value of the gross assets acquired was concentrated in the in-process research and development intangible assets acquired, the Company concluded that this transaction did not meet the definition of a business combination pursuant to FASB Accounting Standard Codification Topic 805, Business Combinations. As such, the transaction was accounted for as an asset acquisition and the upfront consideration of $45.7 million was expensed to research and development in the third quarter of 2020 as there is no future alternative use for the assets.

Corporate Credit Card Program

In connection with the Company's credit card program, the Company established a letter of credit in 2016 for $2.0 million, which has automatic annual extensions and is fully secured by restricted cash.

Fleet Program

In connection with the Company's fleet program, the Company established a letter of credit for $0.4 million, which has automatic annual extensions and is fully secured by restricted cash.

Legal Proceedings

Between July 19 and August 3, 2018, following negative publicity about NUPLAZID, three purported company stockholders filed putative securities class action complaints (captioned Staublein v. Acadia Pharmaceuticals, Inc., Case No. 18-cv-01647, Stone v. Acadia Pharmaceuticals Inc., Case No. 18-cv-01672, and Barglow v. Acadia Pharmaceuticals Inc., Case No. 18-cv-01812) in the U.S. District Court for the Southern District of California against the Company and certain of its current and former executive officers. Thereafter, several putative lead plaintiffs filed motions to consolidate the cases and to appoint a lead plaintiff. On January 3, 2019, the Court consolidated the cases under the caption In re Acadia Pharmaceuticals Inc. Securities Litigation, Case No. 18-cv-01647, and took the lead plaintiff motions under submission. On February 26, 2019, the Court appointed a lead plaintiff and lead counsel. Lead plaintiff filed a consolidated complaint on April 15, 2019. The consolidated complaint generally alleges that defendants violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 by making materially false and misleading statements regarding the Company's business, operations, and prospects by failing to disclose that adverse events and safety concerns regarding NUPLAZID threatened initial and continuing FDA approval, and by failing to disclose that the Company engaged in business practices likely to attract regulatory scrutiny. The consolidated complaint seeks unspecified monetary damages and other relief. Defendants filed a motion to dismiss the consolidated complaint on June 7, 2019. On June 1, 2020, the Court granted the motion in part and gave lead plaintiff leave to file an amended complaint. On July 16, 2020, lead plaintiff filed the amended complaint. Defendants filed a motion to dismiss the amended complaint on August 28, 2020. Lead plaintiff opposed the motion on September 15, 2020. Defendants' reply in support of the motion to dismiss was filed on November 11, 2020. On March 29, 2021, the Court granted the defendants' motion to dismiss with leave to amend. On April 16, 2021, lead plaintiff filed a third amended complaint. Defendants filed a motion to dismiss the third amended complaint on May 31, 2021. The lead plaintiff opposed the motion on July 12, 2021 and Defendants filed their reply in support of their motion on August 11, 2021. On January 3, 2022, the Court issued an order and judgment dismissing lead plaintiff's third amended complaint without leave to amend and closing the case. The deadline to appeal the order and judgment expired on February 2, 2022.

On February 7, 2020, a purported stockholder of the Company filed a derivative complaint (captioned Barney v. Davis et al., Case No. 20-cv-0238) in the U.S. District Court for the Southern District of California against the Company's directors and certain of the Company's current and former executive officers. The complaint asserts claims for breach of fiduciary duty, waste of corporate assets, and unjust enrichment arising from allegations similar to those in the federal securities class action described above. On September 9, 2020, the Court substituted plaintiffs and re-captioned the case Shumacher v. Davis et al., Case No. 20-cv-0238. On June 23, 2020, a second derivative complaint (captioned Lazarus v. Davis et al., Case No. 20-cv-0843) was filed in the U.S. District Court for the District of Delaware. On September 9, 2020, the Court transferred the Lazarus case to the U.S. District Court for the Southern District of California and re-captioned the case Lazarus v. Davis et al., Case No. 20-cv-1774. On January 15, 2021, the Court consolidated the cases under the name In re ACADIA Pharmaceuticals Inc. Stockholder Derivative Litigation, Case No. 20-cv-0238, appointed lead counsel for the plaintiffs, and designated the complaint in the Shumacher case as the operative complaint. The consolidated case is stayed until the defendants in the federal securities class action answer, or the federal securities class action is dismissed with prejudice and all appeals are exhausted, or any party to the stipulation to stay gives 15 days' written notice that it no longer consents to the voluntary stay. As discussed above, the federal securities class action was dismissed with prejudice on January 3, 2022, and the deadline to appeal that dismissal expired on February 2, 2022.

On July 24, 2020, the Company filed complaints against (i) Aurobindo Pharma Limited and its affiliate Aurobindo Pharma USA, Inc. and (ii) Teva Pharmaceuticals USA, Inc. and its affiliate Teva Pharmaceutical Industries Ltd., and on July 30, 2020, the Company filed complaints against (i) Hetero Labs Limited and its affiliates Hetero Labs Limited Unit-V and Hetero USA Inc., (ii) MSN Laboratories Private Ltd. and its affiliate MSN Pharmaceuticals, Inc., and (iii) Zydus Pharmaceuticals (USA) Inc. and its affiliate Cadila Healthcare Limited. These complaints, which were filed in the United States District Court for the District of Delaware, allege infringement of certain of the Company's Orange Book-listed patents covering NUPLAZID. The cases have been assigned to the Honorable Richard G. Andrews. On September 1, 2020, Aurobindo filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity. On September 22, 2020, the Company filed its answer to Aurobindo's counterclaims. On August 31, 2020, Teva filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity. On September 21, 2020, the Company filed its answer to Teva's counterclaims. On October 5, 2020, Hetero filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity. On October 26, 2020, the Company filed its answer to Hetero's counterclaims. On September 30, 2020, MSN filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity regarding certain of the Company's Orange Book-listed patents covering NUPLAZID. On November 5, 2020, the Company filed its first amended complaint against MSN in the United States District Court for the District of Delaware, alleging infringement of certain of the Company's Orange Book-listed patents covering NUPLAZID. On November 19, 2020, MSN filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity regarding certain of the Company's Orange Book-listed patents covering NUPLAZID. On December 10, 2020, the Company filed its answer to MSN's counterclaims. On November 2, 2020, Zydus filed its answer and counterclaims seeking declaratory judgments of noninfringement and invalidity. On November 23, 2020, the Company filed its answer to Zydus's counterclaims. On December 8, 2020, the parties' joint proposed scheduling order was entered by Judge Andrews. On April 7, 2021, the Company filed its first amended complaints against Hetero and Teva and its second amended complaint against MSN, to include an additional Orange Book-listed patent covering NUPLAZID. On April 8, 2021, the Company filed its first amended complaint against Zydus and on April 9, 2021, the Company filed its first amended complaint against Aurobindo. On April 20, 2021, MSN filed its answer, affirmative defenses, and counterclaims to the Company's second amended complaint, seeking declaratory judgments of noninfringement and invalidity regarding certain of the Company's Orange Book-listed patents covering NUPLAZID. On April 21, 2021, Teva filed its answer, affirmative defenses, and counterclaims to Company's first amended complaint, seeking declaratory judgments of noninfringement and invalidity. On April 22, 2021, Zydus filed its answer, affirmative defenses, and counterclaims to Company's first amended complaint, seeking declaratory judgments of noninfringement and invalidity.

On April 22, 2021, Aurobindo filed its answer, affirmative defenses, and counterclaims to the Company's first amended complaint, seeking declaratory judgments of noninfringement and invalidity. On May 11, 2021, the Company filed its answer to MSN's counterclaims. On May 12, the Company filed its answer to Teva's counterclaims. On May 13, the Company filed its answer to Zydus's counterclaims and its answer to Aurobindo's counterclaims. A joint trial in the matters is scheduled for May 15, 2023. The Company entered into an agreement effective April 22, 2021 with Hetero settling all claims and counterclaims in the litigation. The agreement allows Hetero to launch its generic pimavanserin product on July 27, 2038, subject to certain triggers for earlier launch. The Hetero case was dismissed by joint agreement on May 3, 2021.

On August 27, 2021, the Company filed its second amended complaint against Zydus to include an additional Orange Book-listed patent covering NUPLAZID. On September 10, 2021, Zydus filed its answer, affirmative defenses, and counterclaims to the Company's second amended complaint, seeking declaratory judgments of noninfringement and invalidity. Also on September 10, 2021, the parties filed their Joint Claim Construction Chart. On October 1, 2021, the Company filed its answer to Zydus's counterclaims. On November 30, 2021, the Company filed a stipulation and proposed order to dismiss two of its Orange Book-listed patents covering NUPLAZID against Teva, which was ordered by the Court on December 1, 2021. On January 28, 2022, the parties filed their Joint Claim Construction Brief and Appendix. On January 31, 2022, a joint motion for claim construction was ordered by the Court, setting a claim construction hearing on February 23, 2022. A ruling is expected in the near future.

On April 19, 2021, a purported stockholder of the Company filed a putative securities class action complaint (captioned Marechal v. Acadia Pharmaceuticals, Inc., Case No. 21-cv-0762) in the U.S. District Court for the Southern District of California against the Company and certain of the Company's current executive officers. The complaint generally alleges that defendants violated Sections 10(b) and 20(a) of the Securities Exchange Act of 1934 by making materially false and misleading statements regarding the Company's business, operations, and prospects by failing to disclose that the materials submitted in support of its sNDA seeking approval of pimavanserin for the treatment of hallucinations and delusions associated with dementia-related psychosis contained statistical and design deficiencies and that the FDA was unlikely to approve the sNDA in its current form. The complaint seeks unspecified monetary damages and other relief. On June 21, 2021, five motions for lead plaintiff and lead counsel were filed. Thereafter, four of the five movants either withdrew their motions or filed statements of non-opposition. On September 29, 2021, the Court issued an order designating lead plaintiff and lead counsel. On December 10, 2021, lead plaintiff filed an amended complaint. Defendants filed a motion to dismiss the amended complaint on February 15, 2022.

Management currently believes that none of the foregoing claims or actions pending against the Company as of December 31, 2021 is likely to have, individually or in the aggregate, a material adverse effect on the Company's business, liquidity, financial position, or results of operations. Given the unpredictability inherent in litigation, however, the Company cannot predict the outcome of these matters. The Company is unable to estimate possible losses or ranges of losses that may result from these matters, and therefore it has not accrued any amounts in connection with these matters other than attorneys' fees incurred to date.

10. Leases

The Company leases facilities and certain equipment under noncancelable operating leases that expire at various dates through February 2031. Under the terms of the facilities leases, the Company is required to pay its proportionate share of property taxes, insurance and normal maintenance costs.

In 2015, the Company entered into a master lease agreement giving the Company the ability to lease vehicles under operating leases with initial terms of 36 months from the date of delivery. In 2018, the lease agreement was terminated and a new master lease agreement was entered into with a new vendor giving the Company the ability to lease vehicles under operating leases with initial terms ranging from 12 to 50 months from the date of delivery.

The Company leases facilities and certain equipment under noncancelable operating leases with remaining lease terms of 2.0 year to 9.4 years, some of which include options to extend the lease for up to two five-year terms. These optional periods were not considered in the determination of the right-of-use asset or the lease liability as the Company did not consider it reasonably certain that it would exercise such options.

The operating lease costs were as follows (in thousands):

	Years Ended December 31,		
	2021	2020	2019
Operating lease cost	$ 8,874	$ 6,917	$ 5,155

Supplemental cash flow information related to the Company's leases were as follows (in thousands):

	Years Ended December 31,	
	2021	2020
Cash paid for amounts included in the measurement of lease liabilities:		
Operating cash flows from operating leases	$ 5,303	$ 4,480
Right-of-use assets obtained in exchange for operating lease obligations:	17,272	42,039

The balance sheet classification of the Company's lease liabilities was as follows (in thousands):

	December 31, 2021	December 31, 2020
Operating lease liabilities		
Current portion included in accrued liabilities	$ 8,304	$ 5,087
Operating lease liabilities	56,126	44,460
Total operating lease liabilities	$ 64,430	$ 49,547

Maturities of lease liabilities were as follows (in thousands):

	Operating Leases
Years ending December 31,	
2022	$ 8,520
2023	8,390
2024	8,275
2025	8,355
2026	7,719
Thereafter	36,556
Total lease payments	77,815
Less:	
Imputed interest	(13,385)
Total operating lease liabilities	$ 64,430

Operating lease liabilities are based on the net present value of the remaining lease payments over the remaining lease term. In determining the present value of lease payments, the Company uses its incremental borrowing rate based on the information available at the lease commencement date. As of December 31, 2021 and 2020, the weighted average remaining lease term was 9.0 years and 9.4 years, respectively, and the weighted average discount rate used to determine the operating lease liability was 4.3% and 4.7%, respectively.

In the fourth quarter of 2018, the Company entered into an agreement to lease the 4th and 5th floors of corporate office space in San Diego, California with total minimum lease payments of $50.4 million over an initial term of 10 years and 9 months. In February 2020, the Company entered into the first amendment to the lease agreement to lease the 2nd floor of corporate office space in San Diego, California with total minimum lease payments of $25.3 million over an initial term of approximately 10 years and 7 months. In March 2020, the Company entered into the second amendment to the lease agreement which increased the total minimum lease payments of the original corporate office space to $51.4 million. In the third quarter of 2020, the lease for the 4th and 5th floors of corporate office space commenced and the Company capitalized a right of use asset and related lease liability of $40.3 million. In the first quarter of 2021, the lease for the 2nd floor of corporate office space commenced and the Company capitalized a right of use asset and related lease liability of $19.2 million. In connection with this lease and the amendment, the Company established a letter of credit for $3.1 million, which has automatic annual extensions and is fully secured by restricted cash.

11. Selected Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Summarized quarterly data for the years ended December 31, 2021 and 2020 are as follows (in thousands, except per share data):

	Fiscal Year 2021 Quarters				
	1st	2nd	3rd	4th	Total
Revenues	$ 106,554	$ 115,221	$ 131,612	$ 130,758	$ 484,145
Gross profit[1]	$ 104,369	$ 112,695	$ 127,924	$ 128,314	$ 473,302
Net loss	$ (66,448)	$ (43,871)	$ (14,457)	$ (43,094)	$ (167,870)
Basic and diluted net loss per share[2]	$ (0.42)	$ (0.27)	$ (0.09)	$ (0.27)	$ (1.05)

	Fiscal Year 2020 Quarters				
	1st	2nd	3rd	4th	Total
Revenues	$ 90,068	$ 110,103	$ 120,577	$ 121,007	$ 441,755
Gross profit[1]	$ 87,269	$ 107,204	$ 118,572	$ 118,499	$ 431,544
Net loss	$ (88,023)	$ (42,141)	$ (84,660)	$ (66,760)	$ (281,584)
Basic and diluted net loss per share[2]	$ (0.57)	$ (0.27)	$ (0.05)	$ (0.42)	$ (1.79)

(1) Determined by subtracting cost of product sales from product sales, net.

(2) Net loss per common share, basic and diluted, are computed independently for each quarter and the full year based upon respective average shares outstanding. Therefore, the sum of the quarterly net loss per common share amounts may not equal the annual amounts reported.

12. Subsequent Event

In January 2022, the Company entered a license and collaboration agreement with Stoke Therapeutics, Inc. (Stoke) to discover, develop and commercialize novel RNA-based medicines for potential treatment of severe and rare genetic neurodevelopmental diseases of the CNS. The collaboration includes SYNGAP1 syndrome, Rett syndrome (MECP2), and an undisclosed neurodevelopmental target. For the SYNGAP1 program, the two companies will jointly share global research, development and commercialization responsibilities and share 50/50 in all worldwide costs and future profits. In addition, Stoke is eligible to receive potential development, regulatory, first commercial sales and sales milestones. For the MECP2 program and the undisclosed neurodevelopmental program, the Company acquired an exclusive worldwide license to develop and commercialize MECP2 program and the undisclosed neurodevelopmental program. Stoke will lead research and pre-clinical development activities, while the Company will lead clinical development and commercialization activities. The Company will fund research and pre-clinical development activities related to these two targets and Stoke is eligible to receive potential development, regulatory, first commercial sales and sales milestones as well as tiered royalty payments on worldwide sales starting in the mid-single digit range and escalating to the mid-teens based on revenue levels. Under the terms of the agreement, the Company paid Stoke a $60.0 million upfront payment and may be required to pay up to an additional $907.5 million in milestones as well as royalties on future sales.

SCHEDULE II – Valuation and Qualifying Accounts
(in thousands)

		Additions	Deductions		
	Balance at Beginning of Period	Provision Related to Current Period Sales	Actual Distribution Fees, Discounts and Chargebacks Related to Current Period Sales	Actual Distribution Fees, Discounts and Chargebacks Related to Prior Period Sales	Balance at End of Period
Allowance for distribution fees, discounts and chargebacks:					
For the year ended December 31, 2019	$ 1,840	$ 33,827	$ (31,251)	$ (1,840)	$ 2,576
For the year ended December 31, 2020	$ 2,576	$ 51,684	$ (47,463)	$ (2,576)	$ 4,221
For the year ended December 31, 2021	$ 4,221	$ 72,011	$ (63,544)	$ (4,221)	$ 8,467

Exhibit 10.9

Revised Offer Letter

June 26, 2018

Brendan Teehan
2690 Kelly Knoll Lane
Newbury Park, CA 91320

Dear Brendan:

We are delighted to offer to you the position of Vice President, Insights, Analytics, and Commercial Operations with ACADIA Pharmaceuticals Inc. (the "Company" or "ACADIA"). The start date for your employment with ACADIA will be Monday, July 16, 2018 or other date mutually agreed to by you and your supervisor, Michael Yang. As discussed with you, per Company policy, this offer is subject to satisfactory completion of a background investigation. The following summarizes the terms of our offer:

1. **Base Salary.** Your semi-monthly salary will be $12,708.34 ($305,000.16 annualized). As an employee of ACADIA, you will be expected to abide by the Company's rules and regulations and to devote all of your business time, skill, attention and best efforts to ACADIA business to fulfill the responsibilities assigned to you. Your position is full time and is exempt under the FLSA provision for overtime.

1. **Performance Bonus.** You will be eligible to receive a discretionary annual performance bonus ("Annual Bonus") currently targeted at 30% of your annual base salary but which will be granted in the sole discretion of the Board based upon its evaluation of the Company's and your achievement of such specific performance goals as established by the Board. Your Annual Bonus for 2018, if any, will be pro-rated based on your time at the Company in 2018. You must be an employee of the Company on the date upon which any annual bonus is paid to be eligible for such bonus.

2. **Stock Options.**
   - **(a)** **Initial Grant.** In connection with the commencement of your employment, the Company will recommend that the Board of Directors grant you an option (the "Option") to purchase 70,000 shares of the Company's Common Stock (the "Shares") at an exercise price equal to the fair market value of the common stock on the date of grant, as determined in accordance with the terms of the Company's 2010 Equity Incentive Plan (the "Plan"). All option grants must be approved by the Board of Directors.

   - **(b)** **Vesting.** The Option will vest over four (4) years, with twenty-five percent (25%) of the Shares vesting on the first anniversary of the date of grant and 1/48th of the Shares vesting monthly thereafter on the monthly anniversary of the date of grant, provided that you remain employed by the Company through each vesting installment date.

3. **Severance Benefits.** You will be entitled to participate in our Management Severance Benefit Plan ("Severance Plan") and Change in Control Severance Benefit Plan ("CIC Severance Plan"). A copy of each of these plans is available to you on request and each is also on file with the SEC. The following summaries of these plans is qualified in its entirety by the actual terms of the Severance Plan or CIC Severance Plan, as applicable.

   A. **Severance Plan**. In the event of a qualifying termination of employment and subject to the terms of the Severance Plan, you would receive severance including a lump sum severance payment equal to 50% of the sum of your annual base salary and target bonus and continuation of the group healthcare benefits you were receiving at the time of your termination (subject to the terms of the Company's benefit plans) for a six month period.

B. **Change in Control Severance Plan**. In the event of a qualifying termination of employment, up to one month prior to or within 18 months following certain change in control events, you would be entitled to certain severance payments and benefits as outlined in the CIC Severance Plan. The amount of payments and the type of benefits provided under the Severance Plan include cash severance payments based on base salary and bonus, accelerated vesting of equity awards, and payment for continued coverage under group health plans. These benefits include a lump sum severance payment equal to 50% of the sum of your annual base salary and target bonus and continuation of the group healthcare benefits you were receiving at the time of your termination (subject to the terms of the Company's benefit plans) for a six month period and would supersede the severance benefits under the Severance Plan.

4. **Relocation Expenses.** The Company will provide you, through our third party vendor, assistance with temporary housing, the movement of your household goods and 2 cars to San Diego, CA, and other relocation services, in accordance with ACADIA's relocation allowance guidelines. Your complete relocation assistance program is outlined in the attached Summary of Relocation Assistance. This program will expire 1 year following your employment start date. If you leave the Company for any reason other than a reduction in force, or related lay-off within 2 years of your date of hire, you agree to reimburse the Company the total relocation costs paid by the Company, on a prorated basis, and that you are liable for such repayment amount. You agree that such repayment will be due and payable within 30 days of your termination date.

5. **Benefits.** You will be eligible to participate in the Company's standard benefit plans, which include medical, dental, vision, life, accidental death and dismemberment, and short and long-term disability insurance coverage. You will also be able to utilize a flexible spending arrangement that allows employees the opportunity to pay for certain dependent care and health care related costs with pretax dollars. Note that these plans for new employees are effective as of the 1st of the month following the employment start date and enrollment. Your eligibility and participation in these plans, is, of course, subject to the terms of the plans themselves.

6. **Vacation and Holidays.** You will also receive 20 vacation days each year, accrued monthly and paid holidays in accordance with the Company's annual holiday schedule.

7. **401(k).** You will have the opportunity to participate in the Company's 401(k) plan. This plan currently provides for the Company to match, on a dollar for dollar basis, the employee contributions to the plan up to 5% of the employee's compensation, subject to limitations imposed by the Internal Revenue Service. The Company match is subject to change at the discretion of the Board of Directors. The plan provides for enrollment on the first day of each quarter.

8. **Employee Stock Purchase Plan.** You will have the opportunity to enroll in the Company's Employee Stock Purchase Plan (ESPP), which provides for the purchase of shares of ACADIA common stock through payroll deductions. The ESPP currently provides for twice-annual purchases at a discount of at least 15% to the market price, subject to certain limitations.

9. **Inventions and Non-Disclosure.** You will be required to sign the Inventions and Non-Disclosure Agreement, attached to this letter, as a condition of your employment.

10. **Restrictive Covenants, Trade Secrets and Confidential Information from Current or Prior Employers.** You agree that you will not bring or use any confidential information or trade secrets from current or former employers during your employment with the Company. You have notified the Company of any and all non-compete, non-solicitation, confidentiality or other agreements with your current or former employers that could impact your employment with the Company and, prior to your

start date, you will provide the Company with copies of such agreements. You also agree that you have reviewed the duties and responsibilities of your new position and that no contractual or other restrictions will prevent you from performing those duties.

11. **Authorization to Work.** Federal law requires that you provide the Company with the legally required proof of your identity and authorization to work in the United States. We will furnish you with a list of acceptable documents. This documentation must be provided within three (3) business days of the date your employment begins, or our employment relationship with you may be terminated.

12. **At-Will; Entire Agreement.** Your employment is at-will and for no specified period, and either you or ACADIA may terminate this employment relationship at anytime and for any reason. At all times during your employment, you will be subject to the direction and policies from time to time established by Senior Management and the Company's Board of Directors. The agreement in this letter sets forth our entire understanding regarding your employment and supersedes any other negotiations, written or oral.

We look forward to your joining ACADIA Pharmaceuticals Inc. and believe that it will be a mutually beneficial experience. If you have any questions, please contact me at (858)320-8679. This offer, if not accepted, will expire on Wednesday, June 27, 2018.

Please indicate your agreement with the above terms by signing below and returning to my attention.

Sincerely,

/s/Sheri Mayer

Sheri Mayer
Director, Human Resources Business Partner

Accepted and agreed:

/s/Brendan Teehan	June 26, 2018
Brendan Teehan	Date

Exhibit 10.11

April 28, 2020

Mark Schneyer
55 Round Hill Road
Scarsdale, NY 10583

Dear Mark:

I am delighted to offer you the position of Senior Vice President Business Development and Chief Business Officer with ACADIA Pharmaceuticals Inc. (the "Company" or "ACADIA"). The start date for your employment with ACADIA will be mutually agreed to by you and me. The following summarizes the terms of our offer.

Base Salary: Your semi-monthly salary will be $16,041.67 ($385,000.08 annualized). Your position is full time and is exempt/salaried.

Signing Bonus: The Company will provide you a signing bonus of $80,000.00, subject to applicable income tax withholdings. This bonus will be paid on the first pay period following your date of hire. If, within 24 months of your date of hire, you voluntarily terminate your employment with the Company, or the Company terminates your employment for cause, you agree to pay back the signing bonus in full and that you are liable for such repayment amount. You agree that such repayment will be due and payable within 30 days of your termination date.

Performance Bonus: You will be eligible to receive an annual performance bonus ("Annual Bonus") currently targeted at 35% of your annual base salary but which will be granted in the sole discretion of me and the rest of the Board based upon our evaluation of the Company's achievement of specific performance goals as approved by the Board. As allowed by law, you must be an employee of the Company on the date upon which bonuses are earned to be eligible for such a bonus. Your bonus for the period in which you are hired will be prorated based on your date of hire with the Company.

Equity Award:
a) Initial Grant. In connection with the commencement of your employment, you will be granted an equity award consisting of nonqualified stock options ("Options") and restricted stock units ("RSUs") having a cumulative fair market value at the date of grant of $1,500,000.00 (75 percent of the equity award will be in the form of Options and 25 percent will be RSUs).

b) Vesting. Both the Options and the RSUs will vest over four years, as follows:

- one-quarter (25%) of the Options will vest on the first anniversary of the date of grant, and 1/48th of the Options will vest each month thereafter for the following three years, provided that you remain employed by the Company at each such vesting date; and
- one-quarter (25%) of the RSUs will vest on each of the first, second, third and fourth anniversary of the date of grant, provided that you remain employed by the Company at each such vesting date.

c) Other Terms. The Options and RSUs will be subject to the terms of the Company's 2010 Equity Incentive Plan and the related award notices and agreements, which you must electronically acknowledge and execute.

Severance Benefits: You will be entitled to participate in our Management Severance Benefit Plan ("Severance Plan") and Change in Control Severance Benefit Plan ("CIC Severance Plan"). A copy of each of these plans is available to you on request and each is also on file with the SEC.

Relocation Expenses: The Company will provide you, through our third party vendor, assistance with relocation services, in accordance with ACADIA's Relocation Policy dated December 12, 2019. We will provide to you $250,000.00 for your relocation to be used as you see fit and with no time limitations. While our relocation policy states that cash equivalents are not granted for unused benefits, or an unused portion of a benefit, we will provide to you a one-time exception to this policy in order to allow you with the discretion to use any combination of relocation benefits and cash (including, if you choose, "gross-up" for taxes so long as the cumulative amount we pay does not exceed $250,000) that will facilitate your move from Scarsdale, NY to San Diego, CA.

Benefits: You will be eligible to participate in the Company's standard benefit plans. Note that these plans for new employees are effective on the employment start date and enrollment. Your eligibility and participation in these plans, is, of course, subject to the terms of the plans themselves.

Vacation and Holidays: You will also receive 20 vacation days each year, accrued monthly and paid holidays in accordance with the Company's annual holiday schedule.

401(k): You will have the opportunity to participate in the Company's 401(k) plan. The plan provides for enrollment on a monthly basis.

Employee Stock Purchase Plan: You will have the opportunity to enroll in the Company's Employee Stock Purchase Plan (ESPP), which provides for the purchase of shares of ACADIA common stock through payroll deductions. The ESPP currently provides for twice-annual purchases in May and November.

Inventions and Non-Disclosure: You will be required to sign the Inventions and Non-Disclosure Agreement, attached to this letter, as a condition of your employment.

Restrictive Covenants, Trade Secrets and Confidential Information from Current or Prior Employers: You agree that you will not bring or use any confidential information or trade secrets from current or former employers during your employment with the Company. You agree and acknowledge that you have notified the Company of any and all non-compete, non-solicitation, confidentiality or other agreements with your current or former employers that could impact your employment with the Company and, prior to your start date, you will provide the Company with copies of such agreements. You also agree that you have reviewed the duties and responsibilities of your new position and that no contractual or other restrictions will prevent you from performing those duties.

Authorization to Work: Federal law requires that you provide the Company with the legally required proof of your identity and authorization to work in the United States. We will furnish you with a list of acceptable documents. This documentation must be provided within three (3) business days of the date your employment begins, or our employment relationship with you may be terminated.

At-Will; Entire Agreement: Your employment is at-will and for no specified period, and either you or ACADIA may terminate this employment relationship at any time and for any reason. At all times during

your employment, you will be subject to the direction and policies from time to time established by management and the Company's Board of Directors. The agreement in this letter sets forth our entire understanding regarding your employment and supersedes any other negotiations, written or oral. This offer, if not accepted, will expire 5 days from receipt.

Mark, I am very excited about the prospect of you joining the team!

Please indicate your agreement with the above terms by signing below.

Sincerely,

/s/ Steve Davis

Steve Davis
Chief Executive Officer

Accepted and agreed:

/s/Mark Schneyer	June 26, 2018
Mark Schneyer	Date

Exhibit 21.1

List of Subsidiaries

NAME OF SUBSIDIARY	JURISDICTION OF INCORPORATION
ACADIA Pharmaceuticals A/S	Denmark
ACADIA Pharmaceuticals GmbH	Switzerland
ACADIA Pharma Limited	United Kingdom
CerSci Therapeutics Incorporated	Delaware
Amorsa Therapeutics Inc.	Delaware
Acadia Pharmaceuticals Holdings Inc.	Delaware

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statements (Form S-3 Nos. 333-171722, 333-185639, 333-231220, and 333-248401) of Acadia Pharmaceuticals Inc.,

(2) Registration Statement (Form S-8 No. 333-115956) pertaining to the 1997 Stock Option Plan, 2004 Equity Incentive Plan, and 2004 Employee Stock Purchase Plan of Acadia Pharmaceuticals Inc.,

(3) Registration Statements (Form S-8 Nos. 333-128290, 333-137557, 333-146398, 333-153346, and 333-161057) pertaining to the 2004 Equity Incentive Plan and 2004 Employee Stock Purchase Plan of Acadia Pharmaceuticals Inc.,

(4) Registration Statements (Form S-8 Nos. 333-168667, 333-190400, 333-213109, and 333-232981) pertaining to the 2010 Equity Incentive Plan and the 2004 Employee Stock Purchase Plan of Acadia Pharmaceuticals Inc., and

(5) Registration Statements (Form S-8 Nos. 333-207971, 333-219785, and 333-226834) pertaining to the 2010 Equity Incentive Plan of Acadia Pharmaceuticals Inc.;

of our reports dated February 28, 2022, with respect to the consolidated financial statements and schedule of Acadia Pharmaceuticals Inc. and the effectiveness of internal control over financial reporting of Acadia Pharmaceuticals Inc. included in this Annual Report (Form 10-K) of Acadia Pharmaceuticals Inc. for the year ended December 31, 2021.

/s/ Ernst & Young LLP

San Diego, California
February 28, 2022

EXHIBIT 31.1

CERTIFICATION
Pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934,
as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Stephen R. Davis, certify that:

1. I have reviewed this annual report on Form 10-K for the year ended December 31, 2021 of Acadia Pharmaceuticals Inc.

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

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

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

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

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

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

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

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

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

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

Date: February 28, 2022

/s/ Stephen R. Davis

Stephen R. Davis
Chief Executive Officer
(Registrant's Principal Executive Officer)

EXHIBIT 31.2

CERTIFICATION
Pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934,
as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Mark C. Schneyer, certify that:

1. I have reviewed this annual report on Form 10-K for the year ended December 31, 2021 of Acadia Pharmaceuticals Inc.

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

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

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

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

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

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

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

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

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

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

Date: February 28, 2022

/s/ MARK C. SCHNEYER
Mark C. Schneyer
Executive Vice President, Chief Financial Officer
(Registrant's Principal Financial Officer)

EXHIBIT 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Acadia Pharmaceuticals Inc. (the "Company") on Form 10-K for the period ended December 31, 2021, as filed with the Securities and Exchange Commission on or about the date hereof (the "Report"), I, Stephen R. Davis, President and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. §1350, as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that to the best of my knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"); and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Date: February 28, 2022

/s/ STEPHEN R. DAVIS

Stephen R. Davis
Chief Executive Officer
(Registrant's Principal Executive Officer)

This certification shall not be deemed "filed" for purposes of Section 18 of the Exchange Act or otherwise subject to the liability of Section 18 of the Exchange Act. Such certification shall not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent that the Company specifically incorporates it by reference.

EXHIBIT 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of Acadia Pharmaceuticals Inc. (the "Company") on Form 10-K for the period ended December 31, 2021, as filed with the Securities and Exchange Commission on or about the date hereof (the "Report"), I, Mark C. Schneyer, Executive Vice President and Chief Financial Officer of the Company, certify, pursuant to 18 U.S.C. §1350, as adopted pursuant to §906 of the Sarbanes-Oxley Act of 2002, that to the best of my knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"); and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition of the Company at the end of the period covered by the Report and results of operations of the Company for the period covered by the Report.

Date: February 28, 2022

/s/ MARK C. SCHNEYER
Mark C. Schneyer
Executive Vice President, Chief Financial Officer
(Registrant's Principal Financial Officer)

This certification shall not be deemed "filed" for purposes of Section 18 of the Exchange Act or otherwise subject to the liability of Section 18 of the Exchange Act. Such certification shall not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent that the Company specifically incorporates it by reference.