MARINUS PHARMACEUTICALS INC
Form 10-K
March 07, 2016
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10 K

ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015
TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission file number 001 36576

Marinus Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

| Delaware | 20 0198082 |
| --- | --- |
| (State or other jurisdiction of incorporation or organization) | (I.R.S. Employer Identification No.) |

3 Radnor Corporate Center

100 Matsonford Rd, Suite 304

Radnor, PA 19087

(Address of principal executive offices including zip code)

(484) 801-4670

(Registrant’s telephone number, including area code)

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

| Title of Each Class | Name of Each Exchange on Which Registered |
|---|---|
| Voting Common Stock, par value $0.001 per share | Nasdaq Global Market |

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

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10 K or any amendment to this Form 10 K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non accelerated filer or a smaller reporting company. (Check one):

Large accelerated filer Accelerated filer Non accelerated filer Smaller reporting company

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

The aggregate market value of the Registrant's Common Stock (the only common equity of the registrant) held by non-affiliates for the last business day of the Registrant's most recent completed second fiscal quarter: $81,356,124

The number of shares of the issuer's Common Stock outstanding as of March 7, 2016, was 19,509,220.

Documents Incorporated by Reference

Certain portions, as expressly described in this report, of the registrant's proxy statement for the 2016 Annual Meeting of the Stockholders to be held April 19, 2016 are incorporated by reference into Part III, Items 10 14.

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Cautionary Note Regarding Forward-Looking Statements.

This Annual Report on Form 10-K contains forward-looking statements, within the meaning of the U.S. Private Securities Litigation Reform Act of 1995, that involve substantial risks and uncertainties. In some cases, you can identify forward-looking statements by the words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “might,” “objective,” “ongoing,” “plan,” “predict,” “project,” “potential,” “should,” “will,” or “would,” and or the negative of t or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report on Form 10-K, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- our ability to develop and commercialize ganaxolone;
- status, timing and results of preclinical studies and clinical trials;
- the potential benefits of ganaxolone;
- the timing of seeking regulatory approval of ganaxolone;
- our ability to obtain and maintain regulatory approval;
- our estimates of expenses and future revenue and profitability;
- our estimates regarding our capital requirements and our needs for additional financing;
- our plans to develop and market ganaxolone and the timing of our development programs;
- our estimates of the size of the potential markets for ganaxolone;
- our selection and licensing of ganaxolone;

- our ability to attract collaborators with acceptable development, regulatory and commercial expertise;

- the benefits to be derived from corporate collaborations, license agreements, and other collaborative or acquisition efforts, including those relating to the development and commercialization of ganaxolone;

- sources of revenue, including contributions from corporate collaborations, license agreements, and other collaborative efforts for the development and commercialization of products;

- our ability to create an effective sales and marketing infrastructure if we elect to market and sell ganaxolone directly;

- the rate and degree of market acceptance of ganaxolone;

- the timing and amount or reimbursement for ganaxolone;

- the success of other competing therapies that may become available;

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- the manufacturing capacity for ganaxolone;

- our intellectual property position;

- our ability to maintain and protect our intellectual property rights;

- our results of operations, financial condition, liquidity, prospects, and growth strategies;

- the industry in which we operate; and

- the trends that may affect the industry or us.

You should refer to Part I, Item 1A “Risk Factors” of this Annual Report on this Form 10-K for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report on Form 10-K will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

You should read this Annual Report on Form 10-K and the documents that we reference in this Annual Report on Form 10-K and have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

PART I

Item 1. Business.

Overview

We are a clinical stage biopharmaceutical company focused on developing and commercializing innovative therapeutics to treat epilepsy and neuropsychiatric disorders. Our clinical stage product candidate, ganaxolone, is a CNS selective $GABA_A$ modulator being developed in three different dose forms (intravenous ("IV"), oral capsule and oral liquid) intended to provide more treatment options to adult and pediatric patient populations in both acute and chronic care settings. Ganaxolone acts on the $GABA_A$ receptor, a well characterized target in the brain known for both anti seizure and anti anxiety effects through positive allosteric modulation.

Our Pipeline

We are developing ganaxolone for multiple epilepsy and other neuropsychiatric indications, including the following:

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Our most advanced indication for ganaxolone is as an adjunctive, or add-on, therapy for the treatment of drug-resistant focal onset seizures in adults with epilepsy. A Phase 3 randomized multinational clinical trial utilizing ganaxolone oral capsules is fully enrolled for this indication with top-line data planned for release in the middle of 2016.

We are developing an IV formulation for use in the hospital setting to treat status epilepticus. We are making clinical, regulatory and manufacturing preparations to commence a Phase 1 safety study in healthy volunteers in the first half of 2016.

In addition to our core strategy to seek regulatory approval and commercialize our oral dose forms in focal onset seizures and our IV dose form in status epilepticus, we have initiated and fully enrolled two exploratory Phase 2 studies in pediatric orphan indications for which we believe there is a sound mechanistic rationale for therapeutic benefit and the potential for efficient clinical pathways to commercialization. To that end, we expect to release top-line data from our exploratory studies in both Fragile X Syndrome and PCDH19 pediatric epilepsy, in the first half and middle of 2016, respectively.

Ganaxolone Mechanism of Action

Ganaxolone is a CNS-selective $GABA_A$ modulator and a synthetic analog of allopregnanolone. The effects of allopregnanolone have been studied for over two decades, and its role in controlling seizures and improving anxiety, mood and sleep through positive allosteric modulation of $GABA_A$ receptors is well documented. Despite these positive characteristics, we believe allopregnanolone is not suitable for chronic use due to potential undesired hormonal side effects. Ganaxolone was designed to have the same GABA modulation effects at the $GABA_A$ receptors as allopregnanolone without activation of nuclear (classical) progesterone receptors. Ganaxolone and allopregnanolone differ from other GABA agents by interacting with both the synaptic and extrasynaptic $GABA_A$ receptors at a binding site distinct from benzodiazepines and barbiturates. Seizure protection has been shown with ganaxolone in Phase 2 clinical studies, and unlike other $GABA_A$ receptor modulators, tolerance to ganaxolone's anticonvulsant activity has not been demonstrated.

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Ganaxolone Oral — Drug-Resistant Focal Onset Seizures:

Epileptic seizures are generally described in two major groups, primary generalized seizures and focal onset seizures. Primary generalized seizures begin with a widespread electrical discharge that involves both sides of the brain at once. Focal onset seizures begin with an electrical discharge in one limited area of the brain. Generally, a person is diagnosed as having epilepsy when they have had at least two seizures that do not have a self limiting cause such as a high fever.

We have focused most of our recent clinical development efforts on advancing our outpatient chronic epilepsy indications where oral administration is most convenient. To that end, the most advanced clinical study with ganaxolone is the ongoing multinational Phase 3 study for adjunctive treatment of drug-resistant focal onset seizures. Patients enrolled in the study are being randomized, titrated for up to two weeks and then maintain either placebo or 1,800 mg/day of ganaxolone for twelve weeks. The primary endpoint of this trial is percent change in seizure frequency per month compared to baseline. We are capturing adverse events and other measures of safety as well as responder rate, seizure free status and changes in seizure subtypes. Enrollment in this Phase 3 study is complete with approximately 350 patients enrolled in the registration component of the study. We expect top line data to be announced by mid 2016.

We participated in a successful End of Phase 2 meeting in which the United States Food and Drug Administration (FDA) was in general agreement with our planned path to support registration of ganaxolone for adjunctive treatment of focal onset seizures, which, among other anticipated preclinical and clinical studies, includes a single additional Phase 3 registration study. We and the FDA are also in general agreement on the design, population and primary endpoint for both the ongoing and planned second Phase 3 clinical study. We intend to submit the protocol of the second Phase 3 study to the FDA for a Special Protocol Assessment (SPA).

Market Opportunity

Epileptic seizures require chronic treatment, often over a lifetime. Available antiepileptic drugs (AEDs) are efficacious for many patients, but chronic treatment is complicated by side effects, including cardiovascular risks, liver enzyme induction, kidney stones, behavioral changes, sedation and adverse effects on cognitive function, drug tolerance, and reproductive risk.

Women have the added complication that several currently available AEDs increase the risk to the fetus, including birth defects, lowered IQ and low birth weight. Most of these drugs are labeled by the FDA as a potential risk to the fetus, and three of these drugs (valproate, carbamazepine, phenytoin) have been labeled for use only when justified that the therapeutic need outweighs risk to the fetus based on registry data.

According to Decision Resources, in 2014 approximately five million people were under treatment for epilepsy in the United States, Europe and Japan. Despite the many available AEDs, approximately 30 to 35% of patients do not attain acceptable seizure control either with single drug or multiple drug therapy. Furthermore, medications with significant

side effects or dosing regimens that undermine compliance make it difficult for patients to achieve and maintain seizure free status. For these reasons there is a need for new AEDs with novel mechanisms of action and

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improved side effect profiles that can maintain seizure control with chronic administration for people with drug-resistant epilepsy.

The successful introduction of Vimpat by UCB is the most recent example of market acceptance of a new AED with a novel mechanism. Vimpat was approved in the United States and European Union in 2008, and has reported that it achieved global sales of approximately €471 million in 2014. Several other successfully marketed AEDs experienced similar sales levels with similar duration of time on the market. UCB has reported that it expects Vimpat to achieve over €1.2 billion in peak sales globally.

Our Solution

We believe ganaxolone to be a first-in-class therapy with potential to provide meaningful treatment advantages for adults with focal onset seizures who do not achieve adequate seizure control from, have developed tolerance to, or have safety concerns with currently available medications. We believe ganaxolone, if approved, may provide the following benefits for patients:

Efficacy for patients with drug-resistant focal onset seizures. Our completed Phase 2 clinical trial in patients with drug-resistant focal onset seizures demonstrated that patients who added ganaxolone to their medication regimen experienced a statistically significant reduction in seizures as compared to patients who added placebo. Many patients experienced clinically meaningful seizure reduction compared to their baseline measures.

Improved safety and tolerability profile. Ganaxolone was engineered to be a synthetic analog of a natural molecule, allopregnanolone. Completed preclinical safety studies and Phase 1 and 2 clinical trials involving more than 1,000 subjects show ganaxolone to be generally safe and well-tolerated, without evidence of toxicity to heart, liver, blood or other body systems and without many of the side effects common to other AEDs. We believe this safety profile may make ganaxolone a treatment of choice in antiepileptic polypharmacy regimens.

Potential benefit in anxiety and mood. Based on ganaxolone’s mechanism of action and anecdotal reports from clinical trial patients and caregivers, we believe ganaxolone may provide anxiolytic activity and other behavioral benefits in addition to its anticonvulsive activity. With approximately 50% of epilepsy patients estimated to experience comorbid anxiety and/or depression, we believe an AED with additive anxiolytic and mood benefits, could benefit epilepsy patients with comorbid anxiety and mood disorders.

Improved reproductive toxicity profile. Based on ganaxolone’s mechanism of action, and preclinical and clinical findings to date, we believe ganaxolone will offer a lower risk for reproductive toxicity than many currently available AEDs, which we believe would be an important safety differentiator for women of childbearing age.

Clinical Trials for Epilepsy in Adults

Controlled Phase 2 Clinical Trial for Adjunctive Treatment of Drug- Resistant Focal Onset Seizures (Study 600)

We successfully completed a double-blind, randomized, placebo-controlled, Phase 2 clinical trial in the United States of ganaxolone as an adjunctive treatment in patients with drug-resistant focal onset seizures. In this trial, ganaxolone satisfied the primary efficacy endpoint and was considered to be generally safe and well-tolerated. The study enrolled 147 patients who had been diagnosed with epilepsy on average 25 years prior and 75% of which were taking two or three AEDs to control seizures before they entered the study. Subjects were treated for ten weeks with placebo or ganaxolone as adjunctive treatment to existing therapy and recorded their seizures daily in a diary. Mean baseline seizure frequency was 6.5 and 9.2 seizures per seven days in the ganaxolone and placebo groups, respectively. Subjects gradually increased their daily dose up to 1,500 milligrams per day, or mg/day, over the first two weeks, known as titration or the titration period, followed by maintenance dosing at 1,500 mg/day for eight weeks, known as the maintenance period. The primary efficacy endpoint was change from baseline in weekly seizure frequency. The study delivered a statically significant separation from placebo on the primary endpoint as well as on the secondary endpoint of percent change in seizure frequency. Results of the analysis, using a statistical test (Kruskal-Wallis) that is employed

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when data have non-normal distribution, are presented in the table below:

% Seizure Reduction From Baseline

| | Ganaxolone (n=98) | Placebo (n=49) | Difference | |
|---|---|---|---|---|
| Mean (standard deviation) ..... | −17.6% (48.9) | +2.0% (63.2) | 19.6 | % |
| Median ..... | −26.0% | −10.2% | 15.8 | % |

In the intention-to-treat, or ITT, population, which included all study subjects who took at least one dose of study medication, there was a statistically significant reduction in the percent change in mean weekly seizure frequency in the ganaxolone group, which decreased 17.6% from baseline at week 10, whereas in the placebo group, mean weekly seizure frequency increased by 2.0% compared to baseline at week 10, a difference of 19.6% (p=0.014). The p-value represents the probability that the difference between the two groups is due to chance rather than drug effect, and when that probability is less than 5%, or $p<0.05$, the result is considered statistically significant. In the ganaxolone group median seizure frequency decreased by 26.0%, whereas in the placebo group median seizure frequency decreased by 10.2%, a difference of 15.8%. We believe this effect size for an adjunctive treatment of a highly drug-resistant patient population is consistent with the Phase 2 results for other AEDs that ultimately received FDA approval.

Secondary analyses included assessment of the percentage of subjects with greater than or equal to 50% improvement from baseline, or responder analysis, mean and percent change in seizure frequency from baseline, number of seizure-free days and seizure-free subjects, change in seizure frequency by week, and change from baseline in types of seizures. In general, the results of secondary efficacy analyses supported the primary outcome that subjects treated with ganaxolone showed improved seizure control compared to those treated with placebo. The responder analysis during the maintenance phase of treatment is considered by the EMA to be the primary analysis of a registration trial. In this study, the percent of responders in the ganaxolone group compared to the placebo group in the ITT population were 23.5% and 14.6% (p=0.192) for the titration plus maintenance period, and 26.3% v. 13.0% (p=0.057) for the maintenance period. No gender effect or effect of concomitant medication was observed.

An analysis of the responder data showed that the percent of ganaxolone-treated patients who achieved ≥40% improvement in weekly seizure frequency was nearly twice that of placebo-treated patients (30.5% vs. 16.7%, p=0.07). In addition, significantly more patients treated with ganaxolone achieved ≥30% improvement than the placebo group (43.9% vs. 25%, p=0.027). The study observed no difference in percent change in mean weekly seizure frequency or response rate in patients by gender.

Open Label Extension of Controlled Phase 2 Clinical Trial for Adjunctive Treatment of Drug-Resistant Focal Onset Seizures (Study 601)

Of the subjects in our Phase 2 clinical trial, 95% of eligible subjects continued in a long-term open-label extension where the mean duration of treatment was 39 weeks. The objective of the open-label extension study was to evaluate the long-term safety, tolerability and efficacy of ganaxolone at a target dose of 1,500 mg/day. The primary endpoint was change in seizure frequency at endpoint compared to baseline of the double-blind study, presented as mean and median change. Secondary assessments were similar to those evaluated in the blinded portion of the study.

The mean and median percent reductions in weekly seizure frequency were 14.2% and 23.2% from baseline to endpoint, respectively. In total, 70% of subjects had a reduction in seizure frequency during the study. Importantly, subjects previously randomized to placebo in the double-blind study (Study 600) who were switched to ganaxolone in the open-label study showed mean and median reduction in seizure frequency comparable to patients randomized to ganaxolone in the double-blind study.

Secondary analyses included assessment of responders and seizure free status. Twenty-four percent of subjects met responder criteria at endpoint, defined as a reduction in seizures of 50% or more from baseline, while 43% of those who remained in the study for 52 weeks or more met 50% responder criteria. Subjects in the study reported a mean increase in number of seizure-free days per week of 17.4%, an increase that we believe to be meaningful in the context of the severity and persistence of epilepsy in this drug-resistant population.

Phase 2 Clinical Trial of Monotherapy in Drug Resistant Focal Onset Seizures (Study 104)

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A controlled clinical trial was also conducted to evaluate ganaxolone as monotherapy for focal onset seizures in a drug-resistant population. This double-blind, randomized, placebo-controlled, Phase 2 clinical trial enrolled 52 subjects who were withdrawn from their antiepileptic medications prior to evaluation for surgical treatment of their seizures. The subjects were treated with ganaxolone monotherapy 625 mg three times per day for eight days. The primary efficacy measure was duration of treatment prior to study withdrawal, due to emergence of seizures, as measured from day 2 of the study. In the study, 62% of subjects in the placebo group left the study due to emergence of seizures by day 8, compared with 39% of ganaxolone subjects (p=0.08). Statistical testing of completion rates between the two groups found a statistically significant difference between completion rates in the two groups, with 50% of ganaxolone subjects completing the study compared to 25% of placebo subjects (p=0.04).

Ganaxolone Safety Overview

More than 1,000 subjects have received treatment with ganaxolone ranging in duration from one day to more than two years using doses from 50 to 2,000 mg/day. Ganaxolone was administered in Phase 2 studies to pediatric subjects at doses up to 54 mg/kg and to adult subjects at doses up to 1,875 mg/day. No drug-related deaths occurred in any of these clinical trials, and the majority of adverse events were not medically serious and resolved upon discontinuation of therapy. In the ganaxolone safety database there are no trends of medically important changes in blood chemistry, vital signs, liver function, renal function or cardiovascular parameters in the adult or pediatric populations.

We have completed preclinical safety pharmacology and toxicology testing, including reproductive toxicology. Animal pharmacokinetic and in vitro studies show that ganaxolone is primarily metabolized by the CYP3A family of liver enzymes, a common route of drug metabolism. All in vitro studies have shown ganaxolone has low potential for interaction with other drugs at several multiples of observed human ganaxolone levels. Furthermore, neither ganaxolone nor its metabolites have a ketone ring at the 3-position, a requirement for hormonal activity. In binding studies, ganaxolone has no appreciable affinity for estrogen or progesterone receptors. We found no evidence of changes in blood, liver, kidney or the gastrointestinal systems indicating functional or anatomical adverse effects associated with either single- or multiple-dose treatment with ganaxolone in preclinical safety pharmacology studies, nor have we seen evidence of any end organ toxicity from human clinical studies. We have not detected potential for ganaxolone to cause cellular mutations or carcinogenicity in studies to date. We have initiated a two-year carcinogenicity studies in rats and mice.

In reproductive toxicology studies, ganaxolone did not cause any malformations of the embryo or fetus in rats or mice and did not significantly affect the development of offspring. No changes in sperm parameters were found. We believe these findings are important as all currently marketed AEDs have shown developmental toxicities in animal studies such as fetal death or skeletal abnormalities that indicates a finding of developmental toxicities in animal studies. Valproate, carbamazepine, phenytoin and topiramate have been linked with birth defects in humans, for example, head and facial malformations, and lowered birth weight, at a rate higher than observed in women who did not take these drugs. This association has resulted in labeling for these drugs indicating positive evidence of human fetal risk based on scientific data. Based on ganaxolone’s mechanism and preclinical and clinical findings to date, we intend to seek differentiated labeling for ganaxolone, which indicates animal reproduction studies have failed to demonstrate a risk to the fetus, which we believe would be an important safety differentiator for women of childbearing age.

Clinical Safety Results in Epilepsy

Ganaxolone was considered to be generally safe and well-tolerated in the Phase 2 adjunctive treatment trials in adults with drug-resistant focal onset seizures. The majority of adverse events associated with ganaxolone treatment were related to known CNS effects of GABA, were not assessed as serious and resolved upon discontinuation of therapy. The data did not show any trends of clinically important changes in blood chemistry, vital signs, liver function, renal function or cardiovascular parameters related to ganaxolone treatment.

The most frequent treatment-emergent adverse events, or TEAEs, observed in Study 600 are presented in the table below.

Summary of Most Frequently Reported (> 5% of Subjects) TEAEs by

System Organ Class and Preferred Term (ITT Population)

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| Preferred Term | Ganaxolone (n=98) % | Placebo (n=49) % |
|---|---|---|
| Dizziness | 16.3 | 8.2 |
| Fatigue | 16.3 | 8.2 |
| Somnolence | 13.3 | 2.0 |
| Injury, poisoning and procedural complications | 17.3 | 22.4 |
| Headache | 8.2 | 12.2 |
| Coordination abnormal | 6.1 | 6.1 |
| Convulsion | 5.1 | 8.2 |
| Nasopharyngitis | 5.1 | 10.2 |
| Fall | 5.1 | 12.2 |

The two treatment groups had similar rates of discontinuation due to adverse events (7% ganaxolone, 6% placebo) and similar rates of serious adverse events, or SAEs (5% ganaxolone, 8% placebo), mostly related to the underlying epilepsy. The majority of TEAEs resolved with continued treatment or dose reduction. In contrast to some marketed AEDs, the incidence of behavioral TEAEs (reported as depression, insomnia, affective disorder, confusional state, affect lability, aggression, and anxiety) was similar in the ganaxolone and placebo treatment groups.

Ganaxolone continued to be considered generally safe and well-tolerated in the long-term open-label extension, Study 601, in which 120 subjects received ganaxolone for a mean duration of 39 weeks. The most common adverse events considered related to ganaxolone treatment were fatigue (14%), dizziness (9%) and somnolence, also known as sleepiness (7%). Eleven percent of the subjects discontinued due to one or more adverse events. One SAE out of 17 reported was considered related to ganaxolone treatment, a 59 year old female on 900 mg/day whose liver enzymes were elevated after 57 days of treatment. The enzyme levels returned to normal with a reduction in dose to 600 mg/day. In this long-term open-label study of ganaxolone for adjunctive treatment of focal onset seizures, no new safety concerns were identified during extended treatment with doses up to 1,500 mg/day.

In Study 104, the eight-day monotherapy study of ganaxolone and placebo in presurgical patients, ganaxolone was generally well-tolerated and the profile of adverse events between the two groups was similar. Dizziness, which was reported in four ganaxolone and three placebo subjects, was the most frequent adverse event. One SAE was reported in each group; the ganaxolone subject experienced severe agitation and depression while the placebo subject experienced postictal psychosis. As in the other studies, no clinically meaningful differences between treatment groups were noted in laboratory, vital sign, electrocardiogram, or physical/neurological exam results.

Ongoing and Planned Clinical Trials in Epilepsy

In October 2013 we initiated an international, randomized, placebo-controlled, Phase 2b clinical trial in adult subjects for adjunctive treatment of drug-resistant focal onset seizures (Study 603). In Cohort 1, approximately 50 subjects were randomized to receive either placebo or ganaxolone capsules in a step titration of 1,200 mg/day for four weeks

followed by 1,800 mg/day for four weeks. Blood levels of ganaxolone will be assessed at steady state for each dose level. Subjects from both cohorts enter a one year open label period after the double-blind treatment period.

The study protocol was then amended to meet the requirements for a phase 3 study and Cohort 2 was added to the protocol. In Cohort 2, an additional approximately 350 subjects have been randomized, titrated for to two weeks and then receive either placebo or 1,800 mg/day of ganaxolone for 12 weeks. Cohort 2 is intended to meet the Phase 3 design and statistical power requirements and precedents for the FDA and other regulatory bodies for consideration as one of our adequate and well-controlled studies as part of an FDA or EMA filing package for registration. The primary endpoint of this trial is change in seizure frequency per month compared to baseline of Cohort 2 subjects after 14 weeks of treatment, at the end of the blinded phase of the study. We are capturing adverse events and other measures of safety as well as responder rate, seizure-free status and changes in seizure subtypes. We plan to release top-line data in the middle of 2016.

We participated in a clinical End of Phase 2 meeting, in which the FDA was in general agreement with our

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planned path to support registration of ganaxolone for adjunctive treatment of focal onset seizures, which, among other anticipated preclinical and clinical studies, includes a single additional Phase 3 registration study. We and the FDA are also in general agreement on the design, population and primary endpoint for both the ongoing and planned second Phase 3 clinical study. This planned second Phase 3 study will be a double-blind, randomized fixed-dose study to confirm the efficacy, tolerability and safety of ganaxolone for adjunctive treatment of focal onset seizures in adults. This study, per European guidelines and United States precedents, will enroll similar patients as those in our ongoing trial: adult outpatients with drug-resistant focal onset seizures who require add-on therapy in addition to their current AEDs. The study will contain two or three fixed dose arms of ganaxolone versus placebo for 12 weeks of maintenance therapy. Change in seizure frequency compared to baseline will be the primary outcome measure. We intend to submit the protocol of the second Phase 3 study to the FDA for an SPA.

Ganaxolone is currently formulated as an oral liquid suspension and as a capsule. Study 600 and 601 were conducted with an oral liquid suspension formulation and Study 603 is being conducted with a capsule formulation. Pharmacokinetic studies are being planned to establish relative potency between the capsule and the suspension. Separate pharmacokinetic studies suggest that the capsule is approximately 20% more potent than the suspension.

Ganaxolone IV — Status Epilepticus (SE) - An Orphan Disease:

Overview of SE

SE is an epileptic seizure of prolonged duration of more than five minutes or several seizures within a five minute period where the individual does not recover between seizures. It is a medical emergency associated with significant morbidity and mortality. While SE has no FDA approved treatments, single or combinations of intravenous AED(s) are used to attempt to break the seizures.

We are developing ganaxolone IV for the hospital setting, offering a new mechanism of action for treatment of SE. Patients who continue to experience seizures despite treatment with available AEDs are referred to as having established status epilepticus (“ESE”). According to LexisNexis, there are approximately 45,000 cases of hospitalized ESE treated in the United States annually. ESE patients who do not respond to additional AEDs are generally placed under IV anesthesia as a last resort to attempt to stop the seizures and prevent further damage to the brain and death. ESE patients who do not respond to therapy and are placed in a medically induced coma are referred to as having super refractory status epilepticus (“SRSE”). Morbidity and mortality rates increase for patients that progress from ESE to SRSE.

Mechanism of Action

Ganaxolone is a CNS-selective $GABA_A$ modulator that allosterically modulates both synaptic and extrasynaptic $GABA_A$ receptors. In SE, activity at extrasynaptic receptors are of particular importance since certain synaptic

$GABA_A$ receptors are internalized, and thereby unavailable, as SE progresses. As a result, drugs that target down-regulated receptors, such as benzodiazepines, often are no longer effective in treating SE. Allopregnanolone has shown some early clinical evidence in treating certain SRSE patients. In pre-clinical studies, ganaxolone showed activity at least comparable to allopregnanolone in rat models of benzodiazepine resistant SE.

Planned Clinical Trials for Ganaxolone IV

We recently announced our plans to initiate the clinical phase of our ganaxolone IV program in SE. Data from preclinical studies yielded positive results testing ganaxolone IV in benzodiazepine resistant SE. Ganaxolone IV promoted survival and showed at least comparable reversal of seizures than the endogenous neurosteroid allopregnanolone, in clinically translatable rodent models of SE. The studies were conducted at two separate laboratories using different measurements.

We plan to commence a Phase 1 clinical trial designed to evaluate the safety, tolerability and pharmacokinetics of ganaxolone IV in the first half of 2016 before later initiating a Phase 2/3 clinical trial in a SE patient population. We believe ganaxolone IV offers a new mechanism of action for the treatment of SE that is complemented by our oral dose forms, providing potential for continuity of care as patients transition from hospital to outpatient settings.

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Ganaxolone in PCDH19 Pediatric Epilepsy - An Orphan Disease

Overview of PCDH19 Pediatric Epilepsy

PCDH19 pediatric epilepsy (PCDH19-PE) is a rare and serious epileptic syndrome characterized by early-onset cluster seizures, cognitive and sensory impairment of varying degrees, and psychiatric and behavioral disturbances that mostly manifest in females. Currently, there are no approved therapies for PCDH19-PE.

The epileptic disorder is an X-linked condition caused by a missense mutation in the PCDH19 gene, which encodes for a calcium dependent cell-cell adhesion molecule that is expressed in the central nervous system. Genetic testing is available to determine if a child has the PCDH19 mutation. The mean age of onset of this condition is approximately 10 months. Although formal epidemiologic data is not available, it is suspected that approximately 10% of girls who have seizure onset before five years of age have PCDH19 mutations. We estimate the PCDH19 population to be approximately 3,000 to 5,000 patients in the United States.

Mechanism of Action

PCDH19-PE is caused by a mutation in the PCDH19 gene that results in impairment of GABAergic signaling both at the agonist and receptor levels. There is also indirect evidence linking progesterone/allopregnanolone to the onset and offset of seizures in girls with PCDH19-PE. It has been hypothesized that disturbances in certain neurosteroid hormones, such as allopregnanolone, may be implicated in the molecular pathogenesis of PCDH19-PE. We believe that ganaxolone may be useful in the treatment of PCDH19-PE because it is a synthetic analog of allopregnanolone that can be used to increase GABAergic signaling in these patients. We also believe that data from our previously conducted studies of pediatric seizure disorders, which demonstrated ganaxolone’s ability to treat multiple seizure types and showed a safety profile similar to that seen in adults, supports our rationale to pursue this rare disease as PCDH19-PE patients may experience varying types of seizures.

Ongoing Clinical Trial in Patients with PCDH19 Pediatric Epilepsy

Based upon both proof-of-concept data for ganaxolone in the treatment of drug-resistant pediatric seizures and a mechanistic rationale for providing a therapeutic benefit through increased GABAergic signaling we have initiated an expanded access protocol under our epilepsy investigational new drug application (IND) for an open label trial. This proof-of-concept Phase 2 trial is designed to enroll approximately 10 female pediatric patients between the ages of 2

and 18 years old, with a confirmed PCDH19 genetic mutation. After establishing baseline seizure frequency, patients are being treated with ganaxolone administered as either oral liquid suspension or capsules for up to 26 weeks. The primary endpoint of the study is percent change in seizure frequency per 28 days relative to baseline. We plan to release final top-line data from this study in the middle of 2016.

Clinical Trial in Refractory Pediatric Epilepsy

We also conducted an open-label clinical trial to evaluate ganaxolone as add-on therapy in children with refractory epilepsy of multiple seizure types including focal, absence, epileptic spasms, tonic and tonic-clonic. Forty-five subjects aged 1-13 years were treated at doses of up to 12 mg/kg, three times per day. Of the 29 subjects in the study at Week 8, the primary endpoint, twelve (41%) met responder criteria of having 50% or greater improvement from baseline.

Ganaxolone in Fragile X Syndrome, or FXS - An Orphan Disease

Overview of FXS

FXS is a genetic condition that causes intellectual disability, behavioral and learning challenges and various physical characteristics. Approximately one million individuals in the United States have, or are at risk for developing, a Fragile X associated disorder, with approximately 100,000 people having FXS. According to the Centers for Disease

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Control and Prevention, FXS affects 1 in 3,600 to 4,000 males and 1 in 4,000 to 6,000 females of all races and ethnic groups. Patients with FXS exhibit autism-like symptoms including cognitive impairment, anxiety and mood swings, attention deficit and heightened stimuli. Approximately 7% of women and 18% of men with FXS have seizures.

Treatment approaches focus primarily on supportive care and medications addressing development delays, learning disabilities, and social and behavioral problems caused by the disease. Various classes of medications are used to treat behavioral and mental health conditions associated with FXS. Some patients with FXS benefit from medications that treat attention deficient disorders. Other patients who experience general anxiety, social anxiety and other chronic conditions may benefit from different types of anti-anxiety medications and other neuropsychiatric treatments. People with FXS are affected throughout their lives. Currently, there are no known cures or approved therapies for FXS. Special education and symptomatic treatments are employed to lessen the burden of illness.

Mechanism of Action

FXS arises from a mutation of a gene known as the fmr1 gene in the coding for the Fragile X mental retardation protein. In a mouse model of this gene mutation, certain brain regions show lower levels of the extrasynaptic GABAA receptors and reduction of proteins and enzymes responsible for GABA function. The result of fewer GABAA receptors in these mice include over-sensitivity to noise, anxiety, and seizures. Ganaxolone and other agents that have been shown to improve GABA function have also been shown to improve FXS symptoms in this mouse model. As FXS symptoms may be diagnosed as early as infancy, it would be beneficial for a drug approved to treat FXS to have a safety profile acceptable for use in children as well as adults.

We believe that ganaxolone, with its high-affinity for extrasynaptic GABAA receptors, may increase signaling at existing receptors to normalize GABA function thereby reducing anxiety, hyperactivity and other disabilities associated with this inherited disorder.

Ongoing Clinical Trial (Study 800)

The MIND Institute at the University of California, Davis was awarded a medical research grant from the Department of Defense (“DoD”) to study ganaxolone for treatment of behaviors in children and adolescents with FXS. The MIND Institute, in collaboration with Marinus, is conducting a randomized, placebo-controlled, Phase 2 proof-of-concept clinical trial at UC Davis and a site in Belgium. Approximately 60 subjects have been enrolled and titrated up to a maximum dose of 1,800 mg/day of ganaxolone or placebo over a two-week period followed by four weeks of treatment. At the end of the first treatment period and following a washout period, subjects were crossed over to the other treatment for a similar two-week titration period followed by four weeks of treatment.

The primary objective of the study is to explore safety, tolerability and efficacy of ganaxolone for treatment of anxiety and attention in subjects with FXS. Nine rating scales are being used to assess outcome measures for specific behaviors associated with childhood FXS. We plan to announce top-line results in the first half of 2016.

Our Strategy

Our goal is to maximize the value of ganaxolone as a first in class innovative neuropsychiatric therapy with a portfolio of diversified indications. The key elements of our strategy to achieve this goal include the following:

•Broadening dose forms to acute care setting. Our present ongoing clinical trials utilize our patented nanoparticulate composition administered in oral capsule and liquid suspension dose forms. As a complement to these orally administered dose forms, we are preparing to bring our IV dose form into clinical trials for the treatment of SE. We plan to evaluate ganaxolone IV for the acute care setting for in hospital use and in patient populations that may benefit from both inpatient ganaxolone IV and an outpatient oral form for chronic administration.

•Executing our registration studies and pursue regulatory approval for ganaxolone for adjunctive treatment of focal onset seizures and other epilepsy indications. Building on efficacy established in our

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two completed Phase 2 clinical trials, and a differentiated safety profile as demonstrated in extensive preclinical studies and trials in more than 1,000 subjects, we are executing a clinical program to support a registration filing for ganaxolone for adjunctive treatment of focal onset seizures in adults in the United States, Europe and other major markets. Additionally, if the results from our adjunctive focal onset seizure trials are positive, we plan to develop ganaxolone in other segments of the epilepsy market including for monotherapy and pediatric epilepsy. As a result of its efficacy and safety profile, we believe ganaxolone could be a meaningful treatment for epilepsy patients who do not achieve adequate seizure control or have intolerable adverse events with currently available therapies or have concerns around reproductive toxicity.

•Pursuing orphan disease epilepsy indications for ganaxolone. Within epilepsy, there are several smaller patient populations where a genetic marker associated with the syndrome has been linked to deficits in GABAergic signaling. Increasing GABAergic tone with ganaxolone, a CNS selective $GABA_A$ modulator, might provide benefit. Treatments for these small populations have the potential for more efficient paths to regulatory approval and commercialization. A proof of concept open label Phase 2 clinical trial is ongoing for ganaxolone in patients with PCDH19 pediatric epilepsy and FXS. We may also explore development of ganaxolone in other rare genetic epilepsy indications.

•Expanding non epilepsy indications for ganaxolone. Due to its mechanism of action, we believe ganaxolone has potential for therapeutic benefit in a variety of neuropsychiatric disorders in addition to epilepsy. Evidence from preclinical and clinical studies demonstrates that treatment with an agent similar to naturally occurring allopregnanolone could be of benefit in patients with anxiety, mood, sleep and other neuropsychiatric disorders. A proof of concept clinical trial is ongoing for ganaxolone in patients with FXS and PCDH19 pediatric epilepsy, two conditions where patients experience cognitive impairment, behavior problems and anxiety, in addition to seizures. We may explore development of ganaxolone in other neuropsychiatric disorders and rare disease neurology indications.

•Build on our intellectual property. We believe that our intellectual property around our nanotechnology and other formulation know how creates significant barriers to competition. We have developed most of our technology internally, which provides us with greater control and flexibility and reduces expense. We intend to further expand our intellectual property portfolio through internal development and opportunistic licensing or acquisition of complementary technologies.

## Intellectual Property

The proprietary nature of, and protection for our product candidates and discovery programs and know-how are important to our business. We have sought patent protection in the United States and internationally for ganaxolone synthetic methods and ganaxolone nanoparticles, which are used in oral solid, oral liquid, and intravenous dose formulations, other injectable ganaxolone formulations, and methods of treatment using nanoparticulate ganaxolone formulations. Our policy is to pursue, maintain and defend patent rights whether developed internally or licensed from third parties and to protect the technology, inventions and improvements that are commercially important to the development of our business.

The basis of our intellectual property for ganaxolone nanoparticle formulations was the discovery of a novel composition of ganaxolone nanoparticles and complexing agents that deliver consistent exposure and improved

stability of ganaxolone. This discovery resulted in the issuance of United States and foreign patents, which cover ganaxolone nanoparticle formulations and the use of these formulations for treating seizure disorders. Our patent portfolio for ganaxolone nanoparticle formulations contains seven United States patents, one pending United States patent application, and corresponding foreign patents and patent applications directed to solid and liquid ganaloxone formulations and methods for the making and use thereof. These patents expire in 2026, excluding accounting for possible patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, or for possible pediatric exclusivity. Corresponding foreign patents have been granted in Australia, Canada, Eurasia, Japan, Mexico, South Africa, New Zealand, Singapore and South Korea. Corresponding foreign patent applications are pending in China, Europe, India, Israel, Japan, and Mexico. We have not licensed any rights to practice

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these patents in any of these territories. Pursuant to our agreement with Domain Russia Investments Limited, or DRI, we have assigned patent rights, which rights were subsequently assigned to NovaMedica LLC, whereby we licensed our patents, along with the rights to develop and commercialize ganaxolone, in Russia and certain other eastern European nations.

Our patent portfolio also contains patents issued in Australia, United States, Europe, Japan, Mexico and New Zealand covering our novel and cost effective ganaxolone synthesis process, which expire in 2030, excluding accounting for possible patent term extension under the Hatch-Waxman Act, or for possible pediatric exclusivity. Corresponding foreign patent applications are pending in Brazil, Canada, China, Eurasia, Hong Kong, Israel, India, New Zealand and South Korea. We continue to prosecute applications in additional geographic areas.

We filed two provisional applications in 2015 directed to intravenous ganaxolone formulations and methods of using these formulations to treat refractory epileptic seizures and other disorders. One of these patents has since been converted to a US non-provisional and corresponding Patent Cooperation Treaty (PCT) application. If granted, these patents will expire in 2036, excluding accounting for possible patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984 or the Hatch-Waxman Act.

In addition to patents, we rely upon unpatented trade secrets, know-how and continuing technological innovation to develop and maintain a competitive position. We seek to protect our proprietary information, in part, through confidentiality agreements with our employees, collaborators, contractors and consultants, and invention assignment agreements with our employees and some of our collaborators. The confidentiality agreements are designed to protect our proprietary information and, in the case of agreements or clauses requiring invention assignment, to grant us ownership of technologies that are developed through a relationship with a third party.

General considerations

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify a proprietary position for ganaxolone will depend upon our success in obtaining effective patent claims and enforcing those claims once granted. Our commercial success will depend in part upon not infringing upon the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, obtain licenses, or cease certain activities. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights.

The term of a patent that covers a FDA-approved drug may be eligible for patent term extension, which provides patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension

cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products.

Many pharmaceutical companies, biotechnology companies and academic institutions are competing with us in the field of neuropsychiatric disorders and filing patent applications potentially relevant to our business. Even when a third-party patent is identified, we may conclude upon a thorough analysis, that we do not infringe upon the patent or that the patent is invalid. If the third-party patent owner disagrees with our conclusion and we continue with the business activity in question, we may be subject to patent litigation. Alternatively, we might decide to initiate litigation in an attempt to have a court declare the third-party patent invalid or non-infringed by our activity. In either scenario, patent litigation typically is costly and time-consuming, and the outcome can be favorable or unfavorable.

Collaborations

NovaMedica

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In connection with our Series C convertible preferred stock financing, in December 2012 we entered into a Technology Transfer Agreement, or the Transfer Agreement, with DRI, a significant stockholder of our company. Pursuant to the Transfer Agreement, in exchange for a payment of $100,000, we assigned to DRI certain patents and patents applications in Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine and Uzbekistan, or the Covered Territory, and granted to DRI an exclusive, royalty-free, irrevocable and assignable license under our know-how to develop and commercialize ganaxolone and other products that would infringe our patent rights or use our know-how, or the Covered Products, in the Covered Territory, in the field of uses for any human or animal disease or condition excluding the treatment of unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage, or the Field. Immediately thereafter, we, together with DRI, executed an Assignment and Assumption Agreement, pursuant to which all of DRI's rights and obligations under the Transfer Agreement were transferred to NovaMedica, LLC, or NovaMedica. We agreed to take all action required to register or record the patent transfers to DRI in each country in the Covered Territory and to ensure the assignment of DRI's rights under the Transfer Agreement to NovaMedica. NovaMedica is jointly owned by Rusnano Medinvest LLC, or Rusnano Medinvest, and DRI. RMI Investments, S.á.r.l, a stockholder of ours, is a wholly-owned subsidiary of Rusnano Medinvest.

Under the terms of the Transfer Agreement, NovaMedica, or its permitted transferees or assignees, has the exclusive right within the Covered Territory to manufacture the Covered Products solely for development and commercialization in the Covered Territory in the Field. Until the first commercial sale of a Covered Product within the Covered Territory, NovaMedica will have the right to purchase supplies of the Covered Product from us as are reasonably available to us and as are reasonable and necessary to conduct clinical trials of Covered Product in the Covered Territory, provided that any such purchase does not reasonably interfere with our having sufficient supplies of Covered Products on hand for use in development (including the conduct of clinical trials) or commercialization outside of the Covered Territory. Such purchases will be made on a cost-plus basis. The parties shall enter into the Supply Agreement to supply ganaxolone and/or Covered Product for development in the Covered Territory within 60 calendar days from NovaMedica's request, which we have not yet received.

In accordance with the terms of the Transfer Agreement, on June 25, 2013 we entered into a Clinical Development and Collaboration Agreement, or the Collaboration Agreement, with NovaMedica, pursuant to which we agreed to assist NovaMedica in the development and commercialization of Covered Products in the Covered Territory in the Field. The Collaboration Agreement requires the formation of committees consisting of our representatives and NovaMedica representatives to oversee the general development, day-to-day development work and commercialization of Covered Products in the Field in the Covered Territory. All decisions of these committees must be made by unanimous vote, subject to a dispute resolution process. Under the terms of the Collaboration Agreement, the joint committees will determine a development plan for ganaxolone in clinical trials and a plan for commercialization of ganaxolone. NovaMedica will have sole responsibility for the costs and expenses of obtaining regulatory approval for Covered Products and for commercializing any approved products in the Covered Territory, and NovaMedica will have the right to conduct its own clinical studies in the Covered Territory at its sole expense. NovaMedica also has the right to file applications for approval of Covered Products in the Covered Territory, subject to committee oversight. We have agreed, among other things, to provide NovaMedica with data and regulatory files necessary for it to obtain necessary approvals in the Covered Territory, information relating to applications for regulatory approval of Covered Products, certain commercialization information and to assist NovaMedica in conducting any clinical trials necessary for regulatory approval of Covered Products in the Covered Territory. We also have agreed to provide NovaMedica with certain development know-how and support, including making our clinical development personnel available to provide scientific and technical explanations, consultation and support that may be

reasonably requested by NovaMedica.

NovaMedica is required to reimburse us for any out-of-pocket expenses incurred by us in providing this assistance, except for expenses incurred in our participation on the joint committees. Pursuant to the Collaboration Agreement and the Transfer Agreement, we have agreed to use commercially reasonable efforts to include sites in the Russian Federation in our clinical trial programs for the first indications of the Covered Products at our sole expense. Under the Transfer Agreement, at least 36 months prior to the first commercial sale of a product candidate in the Covered Territory, the parties have agreed to negotiate in good faith a supply agreement pursuant to which we or a third party contract manufacturer authorized by us to manufacture and supply the Covered Products, will supply needed quantities of Covered Product to NovaMedica solely for commercialization of Covered Products in the Covered

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Territory, on commercially fair and reasonable terms. Such purchases will be made on a cost-plus basis. In the event the parties are unable to agree on pricing under the supply agreement, they have agreed to engage an internationally recognized consulting firm reasonably acceptable to both parties to perform an analysis to determine final pricing under the supply agreement, which decision will be binding upon the parties. In the event that the parties are unable to reach a reasonably acceptable supply agreement or we are unable to supply Covered Products to NovaMedica under such supply agreement for a period of at least 60 calendar days after the specified delivery date and we thereafter fail to cure such failure within 60 days after written notice from NovaMedica, we have agreed to cooperate with NovaMedica to identify a mutually acceptable alternative source of supply and will provide the necessary consents to allow such alternative source of supply to provide the needed quantities of the Covered Products to NovaMedica. The terms of the alternative source of supply would be negotiated directly by NovaMedica with the supplier.

The Collaboration Agreement expires on the earlier of three years following the first commercial sale of a product candidate in the Covered Territory and terminates upon the termination of the Transfer Agreement. NovaMedica also has the right to terminate the Collaboration Agreement at any time at its convenience upon 90 days' prior written notice.

Purdue

In September 2004, we entered into a license agreement with Purdue, which was most recently amended and restated in May 2008 that granted us exclusive rights to certain know-how and technology relating to ganaxolone, excluding the field of treatment of unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The agreement contains a right by us to sublicense subject to prior written approval by Purdue. We are obligated to pay royalties as a percentage in the range of high single digits up to 10% of net product sales for direct licensed products, such as ganaxolone. The obligation to pay royalties expires, on a country-by-country basis, ten years from the first commercial sale of a licensed product in each country. Upon commercialization, in licensed technology would result in a likely payment burden in the low single digits as a percentage of sales. Other payment obligations may be triggered if we successfully partner our product candidates with third parties. In addition, the agreement also requires that we pay Purdue a percentage in the mid-single digits of the non-royalty consideration that we receive from a sublicensee and a percentage in the twenties of milestone payments for indications other than seizure disorders and vascular migraine headaches not associated with mood disorders. Under the license agreement, we are committed to use commercially reasonable efforts to develop and commercialize at least one licensed product.

Competition

The pharmaceutical industry is highly competitive and subject to rapid and significant technological change. While we believe that our development experience and scientific knowledge provide us with competitive advantages, we face competition from both large and small pharmaceutical and biotechnology companies, specifically with companies that treat neuropsychiatric disorders.

There are a variety of available therapies marketed for neuropsychiatric disorders. In many cases, these products are administered in combination to enhance efficacy or to reduce side effects. Some of these drugs are branded and subject to patent protection, some are in clinical development and not yet approved, and others are available on a generic basis. Many of these approved drugs are well established therapies or products and are widely accepted by physicians, patients and third-party payers. Insurers and other third-party payers may also encourage the use of generic products. More established companies have a competitive advantage over us due to their greater size, cash flows and institutional experience. Compared to us, many of our competitors have significantly greater financial, technical and human resources.

Our competitors may also develop drugs that are safer, more effective, more widely used and less costly than ours, and may also be more successful than us in manufacturing and marketing their products. These appreciable advantages could render ganaxolone obsolete or non-competitive before we can recover the expenses of ganaxolone's development and commercialization.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources

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being concentrated among a smaller number of our competitors. Smaller and other early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and subject registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Competitive Landscape

We primarily compete with pharmaceutical and biotechnology companies that are developing therapies or marketing drugs to treat indications that we are targeting.

Epileptic Seizures

Currently available AEDs control seizures through a variety of mechanisms, including modulation of voltage-activated sodium channels, voltage-activated calcium channels, increasing GABA signaling, and interactions with 2- protein or synaptic vesicle protein SV2A. There are more than 15 approved AEDs available in the United States and worldwide. The top prescribed AEDs include the generic products levetiracetam, lamotrigine, carbamazepine, oxcarbazepine, valproic acid and topiramate. Decision Resources reports that these AEDs are used to treat a substantial percentage of epilepsy patients. Recent market entrants include Vimpat (UCB), Potiga (GlaxoSmithKline), Fycompa (Eisai), and Aptiom (Sunovion Pharmaceuticals). In addition to ganaxolone there are two new chemical entities in late stage development that we are aware of, brivaracetam (UCB), recently approved by FDA, and carisbamate (SK Life Science).

SE

SE patients generally are treated with benzodiazepine as first-line treatment. When benzodiazepines are not effective, several AEDS are used. When second-line AEDs are not effective, the patient is generally placed under IV anesthesia as a last resort to attempt to stop the seizures and prevent further damage to the brain and death. Morbidity and mortality rates increase for patients that progress to SRSE. Sage Therapeutics is developing SAGE-547, an intravenous formulation of allopregnanolone for super-refractory status epilepticus.

PCDH19-PE

There are no drugs approved for the treatment of PCDH19-FPE. PCDH19-FPE patients are typically prescribed drugs approved for epileptic seizures, which often times fail to control seizures in this patient population.

FXS

There are no drugs approved for the treatment of behavioral and mental health conditions associated with FXS although various classes of medications are used off-label. Some patients with FXS benefit from medications that treat attention deficient disorders and other patients who experience general anxiety, social anxiety and other chronic conditions may benefit from different types of anti-anxiety medications.

We are aware of several drugs in development including a number of generic drugs used for other indications such as donepezil, memantine, sertraline, and minocycline. Companies developing compounds include Alcobra, Sunovion Pharmaceuticals, Afraxis and Neuren Pharmaceuticals.

Manufacturing

Manufacturing of drugs and product candidates, including ganaxolone, must comply with FDA current good manufacturing practice, or cGMP, regulations. Ganaxolone is a synthetic small molecule made through a series of organic chemistry steps starting with commercially available organic chemical raw materials. We conduct manufacturing activities under individual purchase orders with independent contract manufacturing organizations, or CMOs, to supply our clinical trials. We have an internal quality program and have qualified and signed quality agreements with our CMOs. We conduct periodic quality audits of their facilities. We believe that our existing suppliers of ganaxolone’s

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active pharmaceutical ingredient and finished product will be capable of providing sufficient quantities of each to meet our clinical trial supply needs. Other CMOs may be used in the future for clinical supplies and, subject to approval, commercial manufacturing.

Ganaxolone Formulations

The therapeutic possibilities of ganaxolone have been understood for some time, however, because ganaxolone is a high-dose water insoluble compound, developing a formulation that could provide consistent drug exposure and could be manufactured at a commercially feasible cost had proven challenging. We believe the discovery of our patented nanoparticulate formulation and novel manufacturing process for ganaxolone address the pharmacokinetic and cost of manufacturing challenges that previously encumbered the clinical and commercial feasibility of ganaxolone.

Ganaxolone is currently formulated as an IV, liquid suspension and as a capsule. We are planning a pharmacokinetic study to establish relative potency between the oral suspension to the capsule. We are presently conducting clinical, regulatory and manufacturing activities to bring our intravenous dose form into the clinic.

Commercial Operations

If we obtain FDA approval for ganaxolone as an adjunctive treatment for patients with focal onset seizures we intend to build a sales and marketing infrastructure to reach high prescribing neurologist and epilepsy specialists in the United States. We believe a focused sales and marketing organization for epilepsy could be leveraged to market ganaxolone in other neurology or psychiatry indications if we are able to obtain regulatory approval for those other indications. We may seek co-promotion partners for our sales efforts to reach other United States physician groups, such as primary care physicians. We believe that there is significant market opportunity for ganaxolone in epilepsy and other neurological and psychiatric conditions outside of the United States. In order to capitalize on this opportunity, we plan to seek collaborations with pharmaceutical companies that have greater reach and resources by virtue of their size and experience in the field.

Government Regulation

As a clinical stage biopharmaceutical company that operates in the United States, we are subject to extensive regulation by the FDA, and other federal, state, and local regulatory agencies. The Federal Food, Drug, and Cosmetic Act, or the FDC Act, and its implementing regulations set forth, among other things, requirements for the research, testing, development, manufacture, quality control, safety, effectiveness, approval, packaging, labeling, storage, record keeping, reporting, distribution, import, export, advertising and promotion of our products. Although the

discussion below focuses on regulation in the United States, we anticipate seeking approval for, and marketing of, our products in other countries. Generally, our activities in other countries will be subject to regulation that is similar in nature and scope as that imposed in the United States, although there can be important differences. Additionally, some significant aspects of regulation in Europe are addressed in a centralized way through the EMA, but country-specific regulation remains essential in many respects. The process of obtaining regulatory marketing approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and may not be successful.

United States Government Regulation

The FDA is the main regulatory body that controls pharmaceuticals in the United States, and its regulatory authority is based in the FDC Act. Pharmaceutical products are also subject to other federal, state and local statutes. A failure to comply explicitly with any requirements during the product development, approval, or post-approval periods, may lead to administrative or judicial sanctions. These sanctions could include the imposition by the FDA or an institutional review board, or IRB, of a hold on clinical trials, refusal to approve pending marketing applications or supplements, withdrawal of approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution.

The steps required before a new drug may be marketed in the United States generally include:

- completion of non-clinical, or preclinical, studies, animal studies and formulation studies in compliance with the FDA’s good laboratory practice, or GLP, regulations;

- submission to the FDA of an IND to support human clinical testing;

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- approval by an IRB at each clinical site before each trial may be initiated;

- performance of adequate and well-controlled clinical trials in accordance with federal regulations, including requirements for good clinical practices, or GCPs, to establish the safety and efficacy of the investigational product candidate for each targeted indication;

- submission of a new drug application, or NDA, to the FDA;

- satisfactory completion of an FDA Advisory Committee review, if applicable;

- satisfactory completion of an FDA inspection of clinical trial sites to ensure compliance with GCPs;

- satisfactory completion of an FDA inspection of the manufacturing facilities at which the investigational product candidate is produced to assess compliance with cGMP, and to assure that the facilities, methods and controls are adequate; and

- FDA review and approval of the NDA.

Clinical Trials

An IND is a request for authorization from the FDA to administer an investigational product candidate to humans. This authorization is required before interstate shipping and administration of any new drug product to humans that is not the subject of an approved NDA. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin. The FDA may submit questions after the 30-day period and after the trial was allowed to begin. Clinical trials involve the administration of the investigational product candidate to subjects under the supervision of qualified investigators following GCPs, requirements meant to protect the rights and health of subjects and to define the roles of clinical trial sponsors, administrators and monitors. Clinical trials are conducted under protocols that detail the subject inclusion and exclusion criteria, the dosing regimen, the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. Each protocol involving testing on United States subjects and subsequent protocol amendments must be submitted to the FDA as part of the IND. The

informed written consent of each participating subject is required. The clinical investigation of an investigational product candidate is generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined. The three phases of an investigation are as follows:

Phase 1. Phase 1 includes the initial introduction of an investigational product candidate into humans. Phase 1 studies may be conducted in subjects with the target disease or condition or healthy volunteers. These studies are designed to evaluate the safety, metabolism, pharmacokinetic properties, or PKs, and pharmacologic actions of the investigational product candidate in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. During Phase 1 studies, sufficient information about the investigational product candidate's PKs and pharmacological effects may be obtained to permit the design of Phase 2 studies. The total number of participants included in Phase 1 studies varies, but is generally in the range of 20 to 80.

Phase 2. Phase 2 includes the controlled clinical trials conducted to evaluate the effectiveness of the investigational product candidate for a particular indication(s) in subjects with the disease or condition under study, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and safety risks associated with the product candidate. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a limited subject population, usually involving no more than several hundred participants.

Phase 3. Phase 3 studies are controlled clinical trials conducted in an expanded subject population at geographically dispersed clinical trial sites. They are performed after preliminary evidence suggesting

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effectiveness of the investigational product candidate has been obtained, and are intended to further evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the product candidate, and to provide an adequate basis for drug approval. Phase 3 studies usually involve several hundred to several thousand participants. In most cases, the FDA requires two adequate and well controlled Phase 3 studies to demonstrate the efficacy of the drug. A single Phase 3 study with other confirmatory evidence may be sufficient in rare instances where the study is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible.

The decision to terminate development of an investigational product candidate may be made by either a health authority body, such as the FDA or IRB/ethics committees, or by a company for various reasons. The FDA may order the temporary, or permanent, discontinuation of a clinical trial, which is referred to as a clinical hold, at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial subjects. In some cases, clinical trials are overseen by an independent group of qualified experts organized by the trial sponsor, or the clinical monitoring board or data safety monitoring board. This group provides authorization for whether or not a trial may move forward at designated check points. These decisions are based on the limited access to data from the ongoing trial. The suspension or termination of development can occur during any phase of clinical trials if it is determined that the participants or subjects are being exposed to an unacceptable health risk. In addition, there are requirements for the registration of ongoing clinical trials of product candidates on public registries and the disclosure of certain information pertaining to the trials as well as clinical trial results after completion.

A sponsor may be able to request a special protocol assessment, or SPA, the purpose of which is to reach agreement with the FDA on the Phase 3 study protocol design and analysis that will form the primary basis of an efficacy claim. A sponsor meeting the regulatory criteria may make a specific request for an SPA and provide information regarding the design and size of the proposed clinical trial. An SPA request must be made before the proposed trial begins, and all open issues must be resolved before the trial begins. If a written agreement is reached, it will be documented and made part of the record. The agreement will be binding on the FDA and may not be changed by the sponsor or the FDA after the trial begins except with the written agreement of the sponsor and the FDA or if the FDA determines that a substantial scientific issue essential to determining the safety or efficacy of the product candidate was identified after the testing began. An SPA is not binding if new circumstances arise, and there is no guarantee that a study will ultimately be adequate to support an approval even if the study is subject to an SPA.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational product candidate information is submitted to the FDA in the form of an NDA to request market approval for the product in specified indications.

New Drug Applications

In order to obtain approval to market a drug in the United States, a marketing application must be submitted to the FDA that provides data establishing the safety and effectiveness of the product candidate for the proposed indication. The application includes all relevant data available from pertinent preclinical studies and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational product candidate to the satisfaction of the FDA.

In most cases, the NDA must be accompanied by a substantial user fee; there may be some instances in which the user fee is waived. The FDA will initially review the NDA for completeness before it accepts the NDA for filing. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. After the NDA submission is accepted for filing, the FDA begins an in-depth review. The FDA has agreed to certain performance goals in the review of NDAs. Most such applications for standard review product candidates are reviewed within ten to twelve months. The FDA can extend this review by three months to consider certain late-submitted information or information

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intended to clarify information already provided in the submission. The FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP. The FDA may refer applications for novel product candidates which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If, or when, those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks. REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can 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 requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory requirements is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of a new NDA or NDA supplement before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Advertising and Promotion

The FDA and other federal regulatory agencies closely regulate the marketing and promotion of drugs through, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet. A product cannot be commercially promoted before it is approved. After approval, product promotion can include only those claims relating to safety and effectiveness that are consistent with the labeling approved by the FDA. Healthcare providers are permitted to prescribe drugs for “off-label” uses—that is, uses not approved by the FDA and therefore not described in the drug’s labeling—because the FDA does not regulate the practice of medicine. However, FDA regulations impose stringent restrictions on manufacturers’ communications regarding off-label uses. Broadly speaking, a manufacturer may not promote a drug for off-label use, but may engage in non-promotional, balanced communication regarding off-label use under specified conditions. Failure to comply with applicable FDA requirements and restrictions in this area may subject a company to adverse publicity and enforcement action by the FDA, the United States Department of Justice, or DOJ, or the Office of the Inspector General of the United States Department of Health and Human Services, or HHS, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products.

Post-Approval Regulations

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After regulatory approval of a drug is obtained, a company is required to comply with a number of post-approval requirements. For example, as a condition of approval of an NDA, the FDA may require post-marketing testing, including Phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. In addition, as a holder of an approved NDA, a company would be required to report adverse reactions and production problems to the FDA, to provide updated safety and efficacy information, and to comply with requirements concerning advertising and promotional labeling for any of its products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval to assure and preserve the long term stability of the drug product. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes extensive procedural and substantive record keeping requirements. In addition, changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose documentation requirements upon a company and any third-party manufacturers that a company may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of ganaxolone. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing.

Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

The Hatch-Waxman Amendments to the FDC Act

Orange Book Listing

In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent whose claims cover the applicant's product or a method of using the product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA, or 505(b)(2) application. An ANDA provides for marketing of a drug product that has the same active ingredients,

generally in the same strengths and dosage form, as the listed drug and has been shown through PK testing to be bioequivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are generally not required to conduct, or submit results of, preclinical studies or clinical tests to prove the safety or effectiveness of their drug product. 505(b)(2) applications provide for marketing of a drug product that may have the same active ingredients as the listed drug and contains full safety and effectiveness data as an NDA, but at least some of this information comes from studies not conducted by or for the applicant. Drugs approved in this way are commonly referred to as “generic equivalents” to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA or 505(b)(2) applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA’s Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. The ANDA or 505(b)(2) applicant may also elect to submit a statement certifying that its proposed ANDA label does not contain (or carves out) any language regarding a patented method of use rather than certify to such listed method of use patent. If the applicant does not challenge the listed patents by filing a certification that the listed patent is invalid or will not be infringed by the new product, the ANDA or 505(b)(2) application will not be approved

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until all the listed patents claiming the referenced product have expired.

A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. If the ANDA or 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA or 505(b)(2) application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) application until the earliest of 30 months, expiration of the patent, settlement of the lawsuit, and a decision in the infringement case that is favorable to the ANDA or 505(b)(2) applicant.

The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired.

Marketing Exclusivity

Upon NDA approval of a new chemical entity, which is a drug that contains no active moiety that has been approved by the FDA in any other NDA, that drug receives five years of marketing exclusivity during which the FDA cannot approve any ANDA seeking approval of a generic version of that drug. Certain changes to a drug, such as the addition of a new indication to the package insert, are associated with a three-year period of exclusivity during which the FDA cannot approve an ANDA for a generic drug that includes the change.

An ANDA may be submitted one year before marketing exclusivity expires if a Paragraph IV certification is filed. In this case, the 30 months stay, if applicable, runs from the end of the five years marketing exclusivity period. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA may be filed before the expiration of the exclusivity period.

Patent Term Extension

After NDA approval, owners of relevant drug patents may apply for up to a five year patent extension. The allowable patent term extension is calculated as half of the drug's testing phase—the time between an effective IND and NDA submission—and all of the review phase—the time between NDA submission and approval up to a maximum of five years. The time can be shortened if the FDA determines that the applicant did not pursue approval with due diligence. The total patent term after the extension may not exceed 14 years.

Many other countries also provide for patent term extensions or similar extensions of patent protection for pharmaceutical products. For example, in Japan, it may be possible to extend the patent term for up to five years and in Europe, it may be possible to obtain a supplementary patent certificate that would effectively extend patent protection for up to five years.

The Foreign Corrupt Practices Act

The Foreign Corrupt Practices Act, or FCPA, prohibits any United States individual or business from paying, offering, or authorizing payment or offering of anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with accounting provisions requiring such companies to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

European and Other International Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products. Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign

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countries prior to the commencement of clinical trials or marketing of the product in those countries. Some countries outside of the United States have a similar process that requires the submission of a request for a clinical trial authorization, or CTA, much like the IND prior to the commencement of human clinical trials. In Europe, for example, a request for a CTA must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA request is approved in accordance with a country's requirements, clinical trial development may proceed.

To obtain regulatory approval to commercialize a new drug under European Union regulatory systems, we must submit a marketing authorization application, or MAA. The MAA is similar to the NDA, with the exception of, among other things, country-specific document requirements.

For other countries outside of the European Union, such as countries in Eastern Europe, Russia, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. Internationally, clinical trials are generally required to be conducted in accordance with GCP, applicable regulatory requirements of each jurisdiction and the medical ethics principles that have their origin in the Declaration of Helsinki.

Compliance

During all phases of development (pre- and post-marketing), failure to comply with applicable regulatory requirements may result in administrative or judicial sanctions. These sanctions could include the FDA's imposition of a clinical hold on trials, refusal to approve pending applications, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, product detention or refusal to permit the import or export of products, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

Other Special Regulatory Procedures

Orphan Drug Designation

The FDA may grant Orphan Drug Designation to drugs intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or, if the disease or condition affects more than 200,000 individuals in the United States, there is no reasonable expectation that the cost of developing and making the drug would be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products grants Orphan Drug Designation to promote the development of products that are intended for the diagnosis,

prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than five in 10,000 persons in the European Union community. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life- threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug.

In the United States, Orphan Drug Designation entitles a party to financial incentives, such as opportunities for grant funding towards clinical trial costs, tax credits for certain research and user fee waivers under certain circumstances. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to seven years of market exclusivity, which means the FDA may not approve any other application for the same drug for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition.

In the European Union, Orphan Drug Designation also entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following drug approval. This period may be reduced to six years if the Orphan Drug Designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Orphan drug designation must be requested before submission of an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of the regulatory review and approval

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process.

Priority Review (United States) and Accelerated Review (European Union)

Based on results of the Phase 3 study(ies) submitted in an NDA, upon the request of an applicant, a priority review designation may be granted to a product by the FDA, which sets the target date for FDA action on the application at six months from FDA filing. Priority review is given where preliminary estimates indicate that a product, if approved, has the potential to provide a safe and effective therapy where no satisfactory alternative therapy exists, or a significant improvement compared to marketed products is possible. If criteria are not met for priority review, the standard FDA review period is ten months from FDA filing. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the Centralized Procedure in the European Union, the maximum timeframe for the evaluation of a MAA is 210 days (excluding “clock stops,” when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee for Medicinal Products for Human Use, or CHMP). Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, defined by three cumulative criteria: the seriousness of the disease (e.g., heavy disabling or life-threatening diseases) to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days.

Healthcare Reform

In March 2010, President Obama signed one of the most significant healthcare reform measures in decades. The Patient Protection and Affordable Care Act and the Health Care and Education Reconciliation Act of 2010, or Affordable Care Act, substantially changes the way healthcare will be financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry. The Affordable Care Act will impact existing government healthcare programs and will result in the development of new programs. For example, the Affordable Care Act provides for Medicare payment for performance initiatives and improvements to the physician quality reporting system and feedback program.

Among the Affordable Care Act’s provisions of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any covered entity engaged in manufacturing or importing certain branded prescription drugs and biological products, apportioned among such entities in accordance with their respective

market share in certain government healthcare programs;

an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, retroactive to January 1, 2010, to 23.0% and 13.0% of the average manufacturer price, or AMP, for most branded and generic drugs, respectively;

expansion of healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;

a new partial prescription drug benefit for Medicare recipients, or Medicare Part D, coverage gap discount program, in which manufacturers must agree to offer 50.0% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;

extension of manufacturers' 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 additional individuals beginning in 2014 and by adding new mandatory eligibility categories for individuals with income at or below 133.0% of the Federal Poverty Level, thereby potentially increasing manufacturers' Medicaid rebate liability;

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expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

new requirements to report annually specified financial arrangements with physicians and teaching hospitals, as defined in the Affordable Care Act and its implementing regulations, including reporting any "payments or transfers of value" made or distributed to physicians and teaching hospitals,and reporting any ownership and investment interests held by physicians and their immediate family members and applicable group purchasing organizations during the preceding calendar year, with data collection to be required beginning August 1, 2013 and reporting to the Centers for Medicare and Medicaid Services, or CMS, to be required by March 31, 2014 and by the 90th day of each subsequent calendar year;

a new requirement to annually report drug samples that manufacturers and distributors provide to physicians;

a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and

a mandatory nondeductible payment for employers with 50 or more full-time employees (or equivalents) who fail to provide certain minimum health insurance coverage for such employees and their dependents, beginning in 2015 (pursuant to relief enacted by the Treasury Department).

The Affordable Care Act also establishes an Independent Payment Advisory Board, or IPAB, to reduce the per capita rate of growth in Medicare spending. Beginning in 2014, IPAB is mandated to propose changes in Medicare payments if it determines that the rate of growth of Medicare expenditures exceeds target growth rates. The IPAB has broad discretion to propose policies to reduce expenditures, which may have a negative impact on payment rates for pharmaceutical products. A proposal made by the IPAB is required to be implemented by CMS unless Congress adopts a proposal with savings greater than those proposed by the IPAB. IPAB proposals may impact payments for physician and free-standing services beginning in 2015 and for hospital services beginning in 2020.

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. In August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend proposals in spending reductions to Congress. The Joint Select Committee did not achieve its targeted deficit reduction of an amount greater than $1.2 trillion for the years 2013 through 2021, triggering the legislation's automatic reductions to several government programs. These reductions include aggregate reductions to Medicare payments to healthcare providers of up to 2.0% per fiscal year, starting in 2013. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several categories of healthcare providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material

adverse effect on our customers and accordingly, our financial operations.

We anticipate that the Affordable Care Act will result in additional downward pressure on coverage and the price that we receive for any approved product, and could seriously harm our business. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. In addition, it is possible that there will be further legislation or regulation that could harm our business, financial condition and results of operations.

Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for which we receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third-party payers. Third-party payers include government health administrative authorities, managed care providers, private health

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insurers and other organizations. The process for determining whether a payer will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the drug product. Third-party payers may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Third-party payers are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA approvals. Ganaxolone may not be considered medically necessary or cost-effective. A payer's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In 2003, the United States Congress enacted legislation providing Medicare Part D, which became effective at the beginning of 2006. Government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, to obtain payments under this program, we would be required to sell products to Medicare recipients through prescription drug plans operating pursuant to this legislation. These plans will likely negotiate discounted prices for our products. Federal, state and local governments in the United States continue to consider legislation to limit the growth of healthcare costs, including the cost of prescription drugs. Future legislation could limit payments for pharmaceuticals such as the product candidates that we are developing.

Different pricing and reimbursement schemes exist in other countries. In the European Union, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national healthcare systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed upon. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become more intense. As a result, increasingly high barriers are being erected to the entry of new products. 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 for ganaxolone from lower-priced products in foreign countries that have placed price controls on pharmaceutical products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payers fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time.

Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Compliance Requirements

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand and prescribers, purchasers, and formulary managers on the other. Although there are a number of statutory exemptions and regulatory safe harbors protecting some business arrangements from prosecution, the exemptions and safe harbors are drawn narrowly and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exemption or safe harbor. Our practices may not

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in all cases meet all of the criteria for safe harbor protection from federal Anti-Kickback Statute liability. The reach of the Anti-Kickback Statute was broadened by the Affordable Care Act, which, among other things, amends the intent requirement of the federal Anti-Kickback Statute. Pursuant to the statutory amendment, a person or entity no longer needs to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the Affordable Care Act provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the civil False Claims Act (discussed below) or the civil monetary penalties statute, which imposes penalties against any person who is determined to have presented or caused to be presented a claim to a federal health program that the person knows or should know is for an item or service that was not provided as claimed or is false or fraudulent.

The federal False Claims Act prohibits any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using, or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. As a result of a modification made by the Fraud Enforcement and Recovery Act of 2009, a claim includes "any request or demand" for money or property presented to the United States government. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of the product for unapproved, and thus non-reimbursable, uses. The Health Insurance Portability and Accountability Act of 1996, or HIPAA, created new federal criminal statutes that prohibit knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third-party payers and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payer.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by The Health Information Technology for Economic and Clinical Health Act, or HITECH, and its implementing regulations, imposes requirements relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's privacy and security standards directly applicable to "business associates"—independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service on behalf of a covered entity. HITECH also increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

In the United States our activities are potentially subject to additional regulation by various federal, state and local authorities in addition to the FDA, including CMS, other divisions of HHS (for example, the Office of Inspector General), the DOJ and individual United States Attorney offices within the DOJ, and state and local governments. If a drug product is reimbursed by Medicare or Medicaid, pricing and rebate programs must comply with, as applicable, The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or Medicare Modernization Act, as

well as the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990, or the OBRA, and the Veterans Health Care Act of 1992, or the VHCA, each as amended. Among other things, the OBRA requires drug manufacturers to pay rebates on prescription drugs to state Medicaid programs and empowers states to negotiate rebates on pharmaceutical prices, which may result in prices for our future products that will likely be lower than the prices we might otherwise obtain. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. Under the VHCA, drug companies are required to offer some drugs at a reduced price to a number of federal agencies including the United States Department of Veterans Affairs and the DoD, the Public Health Service and some private Public Health Service designated entities in order to participate in other federal funding programs including Medicaid. Recent legislative changes require that discounted prices be offered for specified DoD purchases for its TRICARE program via a rebate system. Participation under the VHCA requires submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulation.

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Because of the breadth of these laws and the narrowness of available statutory and regulatory exemptions, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including criminal and significant civil monetary penalties, damages, fines, imprisonment, exclusion from participation in government programs, injunctions, recall or seizure of products, total or partial suspension of production, denial or withdrawal of pre-marketing product approvals, private "qui tam" actions brought by individual whistleblowers in the name of the government or refusal to allow us to enter into supply contracts, including government contracts, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that any of our products are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, and implementation of corporate compliance programs and reporting of payments or transfers of value to healthcare professionals.

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 some 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. In addition, in November 2013, the Drug Quality and Security Act became law and establishes requirements to facilitate the tracing of prescription drug products through the pharmaceutical supply distribution chain. This law includes a number of new requirements that will be implemented over time and will require us to devote additional resources to satisfy these requirements. Several states have enacted legislation requiring pharmaceutical companies to, among other things, establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing specified physician prescribing data to pharmaceutical companies for use in sales and marketing, and to prohibit other specified sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

Research and Development

Conducting research and development is central to our business model. We have invested and expect to continue to invest significant time and capital in our research and development operations. Our research and development expenses were $18.9 million and $8.7 million in 2015 and 2014, respectively.

Employees

As of December 31, 2015, we had 11 full-time employees and one part time employee. In addition to our employees, we contract with third-parties for the conduct of certain clinical development, manufacturing, accounting and administrative activities. We anticipate increasing our head count. We have no collective bargaining agreements with our employees and none are represented by labor unions.

Corporate Information

We were incorporated in Delaware in August 2003. Our principal executive offices are located at 3 Radnor Corporate Center, 100 Matsonford Rd, Suite 304, Radnor, Pennsylvania 19087 and our telephone number is (484) 801-4670. Our website address is www.marinuspharma.com. The inclusion of our website address is, in each case, intended to be an inactive textual reference only and not an active hyperlink to our website. The information contained in, or that can be accessed through, our website is not part of this Annual Report on Form 10-K.

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Item 1A. Risk Factors.

We have a limited operating history, have incurred significant losses since our inception and anticipate that we will continue to incur losses in the future.

We commenced operations in 2003, and we have only a limited operating history upon which you can evaluate our business and prospects. Our operations to date have been limited to conducting product development activities for ganaxolone and performing research and development with respect to our clinical and preclinical programs. In addition, as a clinical stage biopharmaceutical company, we have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. Nor have we demonstrated an ability to obtain regulatory approval to commercialize any of our product candidates. Consequently, any predictions about our future performance may not be as accurate as they would be if we had a history of successfully developing and commercializing biopharmaceutical products.

We have incurred significant operating losses since our inception, including net losses of $24.9 million for the year ended December 31, 2015. As of December 31, 2015, we had an accumulated deficit of $97.2 million. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. Our losses have resulted principally from costs incurred in our research and development activities. We anticipate that our operating losses will substantially increase over the next several years as we execute our plan to expand our research, development and commercialization activities, including the clinical development and planned commercialization of our product candidate, ganaxolone, and incur the additional costs of operating as a public company. In addition, if we obtain regulatory approval of ganaxolone, we may incur significant sales and marketing expenses. Because of the numerous risks and uncertainties associated with developing biopharmaceutical products, we are unable to predict the extent of any future losses or whether or when we will become profitable, if ever.

We have not generated any revenue to date from product sales. We may never achieve or sustain profitability, which could depress the market price of our common stock, and could cause you to lose all or a part of your investment.

To date, we have no products approved for commercial sale and have not generated any revenue from sales of any of our product candidates, and we do not know when, or if, we will generate revenues in the future. Our ability to generate revenue from product sales and achieve profitability will depend upon our ability to successfully gain regulatory approval and commercialize ganaxolone or other product candidates that we may develop, in-license or acquire in the future. Even if we obtain regulatory approval for ganaxolone, we do not know when we will generate revenue from product sales, if at all. Our ability to generate revenue from product sales from ganaxolone or any other future product candidates also depends on a number of additional factors, including our ability to:

successfully complete development activities, including enrollment of study participants and completion of the necessary clinical trials;

complete and submit NDAs to the FDA and obtain regulatory approval for indications for which there is a commercial market;

complete and submit applications to, and obtain regulatory approval from, foreign regulatory authorities;

make or have made commercial quantities of our products at acceptable cost levels;