PROTOCOL: 1042-PPD-2002

TITLE: **A Phase 2A, Double-blind, Placebo-controlled, Multiple-dose Escalation Study to Evaluate Safety, Pharmacokinetics and Efficacy of Intravenously and Orally Administered Ganaxolone in Women with Postpartum Depression**

DRUG: Ganaxolone (CCD 1042:3α-hydroxy-3β-methyl-5α-pregnan-20-one)

IND: 106,104

SPONSOR:
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INITIAL VERSION (V 1.0):	05 December 2016
AMENDMENT 1 (V 2.0):	15 February 2017
AMENDMENT 2 (V 3.0):	10 October 2017
AMENDMENT 3 (V 4.0):	19 October 2017
AMENDMENT 4 (V 5.0)	01 February 2018
AMENDMENT 5 (V 6.0)	28 February 2018
AMENDMENT 6 (V 7.0)	09 May 2018
AMENDMENT 7 (V 8.0)	08 Oct 2018

PROTOCOL SIGNATURE PAGE

Sponsor's (Marinus) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted] MD [redacted] Clinical Development and Pharmacovigilance	

Investigator's Acknowledgement

I have read this protocol for Marinus Study 1042-PPD-2002.

Title: A Phase 2A, Double-blind, Placebo-controlled, Multiple-dose Escalation Study to Evaluate Safety, Pharmacokinetics and Efficacy of Intravenously and Orally Administered Ganaxolone in Women with Postpartum Depression

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

SERIOUS ADVERSE EVENT REPORTING:

In the event of a serious adverse event (SAE), the investigator must e-mail or fax the Marinus Clinical Study Serious Adverse Event Form within 24 hours to Marinus Safety Department at:

Email: safetyPPD2002@marinuspharma.com

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SPONSOR CONTACTS:

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ABBREVIATIONS

AE	adverse event
ALT	alanine Aminotransferase
AST	aspartate Aminotransferase
BP	blood pressure
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
Cmax	peak plasma concentration
CRF	case report form
CRO	contract research organization
CSSRS	Columbia Suicide Severity Rating Scale
CTNI	Massachusetts General Hospital Clinical Trials Network and Institute
ECG	electrocardiogram
EPDS	Edinburgh Postnatal Depression Scale
FDA	Food and Drug Administration
GABA	gamma Aminobutyric Acid
GCP	Good Clinical Practice
HAMD17	Hamilton Depression Rating Scale 17-item version
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
PK	Pharmacokinetic
PO	Orally
PPD	Postpartum Depression
SAE	serious adverse event
SAP	statistical analysis plan
SNRIs	serotonin and norepinephrine reuptake inhibitors
SRC	safety review committee
SSRIs	selective serotonin reuptake inhibitors
SSS	Stanford Sleepiness Scale
STAI	Spielberger State-Trait Anxiety Inventory

STUDY SYNOPSIS

Protocol number: 1042-PPD-2002	**Drug:** Ganaxolone IV, Ganaxolone Oral Capsules
Title of the study: A Phase 2A, Double-blind, Placebo-controlled, Multiple-dose Escalation Study to Evaluate Safety, Pharmacokinetics and Efficacy of Intravenously and Orally Administered Ganaxolone in Women with Postpartum Depression	
Number of subjects (total and for each treatment arm): This is a Phase 2A, double-blind, placebo-controlled, multiple-dose escalation study consisting of up to 6 cohorts (Cohorts 1-6). Approximately 200 women with PPD 18 to 45 years of age will be screened to randomize up to 100 subjects across up to 6 cohorts. Approximately 10-30 subjects will be randomized into each cohort. Randomized subjects will receive the investigational product (IP), ganaxolone or matching placebo in a 1:1 ratio. In Cohorts 1-5 the IP will be administered intravenously over 60 hours. In Cohort 6 the dosing is initiated with a 6-hour intravenous (IV) infusion followed by oral dosing for 28 days plus 3-day taper.	
Site(s) and Region(s): Approximately 20 investigative sites in the United States	
Study period (planned): March 2017 to June 2019	**Clinical phase:** Phase 2A
Objectives: **Safety objective:** To assess the safety and tolerability of escalating doses of intravenously and orally administered ganaxolone as determined by adverse events and changes from baseline in laboratory measures, vital signs, Columbia Suicide Severity Rating Scale (CSSRS), electrocardiogram (ECG), Stanford Sleepiness Scale (SSS), and physical examination. **Efficacy objective:** To explore the efficacy of escalating doses of intravenously and orally administered ganaxolone in the treatment of PPD with the Hamilton Depression Rating Scale 17-item version (HAMD17), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State-Trait Anxiety Inventory 6-item version (STAI6) and Clinical Global Impression-Improvement (CGI-I) scale. **Pharmacokinetic objective:** To collect samples of blood for pharmacokinetic analysis after administration of IV and oral ganaxolone.	
Rationale: Rapidly declining plasma levels of allopregnanolone and other neurosteroids, after childbirth are thought to be linked to triggering depression in women who are vulnerable to develop this condition. Ganaxolone, a synthetic analog of allopregnanolone, may provide benefit to these women.	
Investigational product, dose, and mode of administration: Ganaxolone IV or IV placebo. **Cohort 1:** ganaxolone is infused at a rate of 4 mg/h (16 ml/h of ganaxolone 0.25 mg/ml solution) for 48 hours and then at a rate of 2 mg/h for the next 12 hours. The infusion is stopped at 60 hours. **Cohort 2:** ganaxolone is infused at a rate of 8 mg/h (16 ml/h of ganaxolone 0.5 mg/ml solution) for 48 hours and then at a rate of 4 mg/h for the next 12 hours. The infusion is stopped at 60 hours. **Cohort 3:** Twelve mg bolus of ganaxolone is initially given over 2 minutes followed by ganaxolone infusion at a rate of 12 mg/h (24 ml/h of ganaxolone 0.5 mg/ml solution) for 48 hours. The rate is then reduced to 6 mg/h for the next 12 hours. The infusion is stopped at 60 hours. **Cohorts 4-5:** Cohorts 4 and 5 are optional and will be utilized only if further dose exploration is warranted. Ganaxolone infusion rate will be decided based on the results of Cohorts 1-3. However, the initial bolus dose will not exceed 16 mg over 2 minutes and the maximum infusion rate will not exceed 16 mg/h. **Cohort 6:** In this cohort dosing is initiated with ganaxolone infusion at a rate of 20 mg/h (40 ml/h of ganaxolone 0.5 mg/ml solution or matching placebo) for 6 hours followed by ganaxolone 900 mg or matching placebo capsules given orally at dinner time for 28 days followed by a 3-day taper.	

Methodology:

The screening period for each cohort will be up to 2 weeks.

For Cohorts 1-5, following the screening period, there will be a 4-day inpatient treatment phase at a hospital or clinical pharmacology unit during which a 60-hour infusion of ganaxolone or placebo will be administered. The subjects will be discharged from the unit on the morning of Day 4. There will be 2 safety follow-up visits after inpatient discharge on post-treatment Weeks 1 and 4.

In Cohort 6, following the screening period, there will be a 1-day inpatient treatment phase at a hospital or clinical pharmacology unit. The study drug will be administered intravenously over a period of 6 hours followed by administration of the first dose of the oral study drug (ganaxolone 900 mg or matching placebo) at dinner time. The subjects will be discharged home the next morning (Day 2), and oral dosing will be continued at home for 27 days (Days 2-28 at dinner time daily followed by a 3-day taper. There will be 3 safety follow-up visits after the last dose on post-treatment Weeks 1, 4, and 6.

Inclusion Criteria:

1. An understanding of and ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
3. Female aged 18 to 45 years, inclusive, at the Screening Visit
4. Experiencing a Major Depressive Episode, which started between the start of the third trimester and 4 weeks following delivery. The Major Depressive Episode must be diagnosed according to MINI 7.0 interview
5. Given birth in the last 12 months
6. HAMD17 score of ≥ 26 at screening (HAMD17 must be ≥ 22 per CTNI rating at Admission to the Unit on Day 0)
7. The diagnosis of PPD and severity of depression must be supported by the SAFER interview
8. Must agree to stop breastfeeding from start of study treatment to 45 days after end of study treatment
9. Must agree to use acceptable contraceptive methods during the study period

Exclusion Criteria

1. Current or past history of any psychotic illness, including Major Depressive Episode with psychotic features
2. Any psychiatric condition that, in the investigator's judgment, is considered clinically significant and could affect subject safety or study outcome including eating disorder, panic disorder, obsessive-compulsive disorder, or post-traumatic stress disorder
3. History of suicide attempt within the past 3 years (actual attempt, interrupted or aborted attempt, preparatory acts or behavior)
4. Active suicidal ideation (e.g. answering "yes" to questions 4 or 5 in the CSSRS suicidal ideation section)
5. History of severe bipolar I disorder (e.g. hospitalization due to the illness, lifetime history of psychosis or suicide attempt)
6. Uncontrolled seizure disorder
7. Current or history within the past 3 years of any substance use disorder, with the exception of tobacco or caffeine

8. Positive drug screen for any illicit substances or prescription drugs at screening or randomization. If the drug screen is positive for a prescription drug that has the potential to be abused (e.g. amphetamine, benzodiazepine), legitimate use of the drug must be verified by the subject's providing the current pill bottle, prescription for the drug, or a note from the prescribing physician. Cannabis use is prohibited, and subjects with positive drug screen for cannabis are excluded. However, occasional users of cannabis may be re-tested if the subject is willing to refrain from consuming cannabis-based products during the trial. If the re-test sample is negative at screening the subject can be considered eligible. If the re-test sample is positive for cannabis the investigator may ask for determination of the urine or blood levels of Δ9-tetrahydrocannabinol (THC), and its metabolites 11-hydroxy-THC and, 9-carboxy-THC. If the levels of THC are not detectable the subject may be considered eligible for the trial.
9. Current or relevant history of any medical disorder that may require treatment or make the subject unlikely to be able to complete the study, or any condition that presents undue risk from the investigational product or procedure point of view
10. Any clinically significant abnormality identified on physical examination, ECG or laboratory tests that in the judgment of the investigator would compromise the subject's safety or successful participation in the clinical study
11. Subject has untreated or uncontrolled hypothyroidism
12. Known or suspected intolerance or hypersensitivity to the investigational product(s) or allopregnanolone, or any of the stated ingredients
13. Use of another investigational product within 60 days prior to the first dose of investigational product
14. Has alanine transferase (ALT) or aspartate transferase (AST) greater than 2.5 times upper limit of normal or total bilirubin greater than 1.5 times upper limit of normal (unless elevation is due to Gilbert's syndrome)
15. Screening QTcF > 470 msec
16. Unwillingness to withhold grapefruit, Seville oranges, star fruit, or citrus derived products from diet between screening and discharge from the study unit
17. Receiving concomitant treatment with strong CYP3A4 inducers or strong CYP3A4 inhibitors
18. Body mass index (BMI) ≥ 40
19. Subject is pregnant
20. Subject is using prohibited medications as specified in Section 5.3.2

Maximum duration of subject involvement in the study: Approximately 12 weeks

Safety: Adverse events, vital signs, Columbia Suicide Severity Rating Scale (CSSRS), electrocardiogram (ECG), Stanford Sleepiness Scale (SSS), and physical examination.

Efficacy: Hamilton Depression Rating Scale (HAMD17), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State-Trait Anxiety Inventory six item version (STAI6) and Clinical Global Impression-Improvement (CGI-I) scale.

Pharmacokinetics: Six samples will be collected for pharmacokinetic analysis in Cohorts 1-5 and 12 samples in Cohort 6. Maximal plasma concentration (C_{max}), concentration at steady-state (C_{ss}, determined by the mean concentrations once steady-state is achieved by visual inspection), AUC_{0-24} (calculated as C_{ss} multiplied by 24 hours) will be estimated. Seven samples will be collected during the inpatient phase of Cohort 6 (including 6 samples on Day 1) followed by collection of 5 samples during the outpatient phase during the study visits for a total of 12 samples in Cohort 6.

Statistical Methods:
Sample size: No formal hypothesis testing will be performed, and the sample size is not based on statistical power considerations. A population of about 6 to 10 subjects per dose is commonly tested in studies which aim to establish a tolerability range for a new compound or a new formulation.

Analysis Populations: The Screened Set will consist of all subjects who have signed an informed consent. The Randomized Set will consist of subjects randomized. The Safety Set will consist of all subjects who received IP. The modified Intent to Treat Set (mITT) will consist of all subjects in the Safety Set who have at least 1 post-baseline efficacy assessment. The Per-Protocol Set will consist of all subjects in the mITT set who do not have major protocol deviations that may affect key efficacy endpoints. The Infusion Completer Set will consist of all subjects in the Safety Set who completed the 60-hour infusion in Cohorts 1-5, and who completed the 6-hour infusion in Cohort 6. The Completer Set will consist of all subjects in the Safety Set who completed the 60-hour infusion and attended the final safety follow-up visit in Cohorts 1-5, and who completed the 6-hour infusion and oral dosing period and attended all outpatient visits including the safety follow-up visits in Cohort 6.

Analysis Methods: Data analyses will primarily be descriptive. Continuous variables will be summarized as numbers of observations, means, measures of variance (e.g., standard deviation), and percentiles (e.g., median, minimum, maximum). Categorical variables will be summarized as numbers of observations and percentages. Results from exploratory statistical analyses of efficacy endpoints may be presented but only to aid in interpretation.

1.0 BACKGROUND INFORMATION

1.1 Postpartum Depression (PPD)

Postpartum depression (PPD) is a mood disorder that occurs in about 7% of women following the birth of a child.[4] Common symptoms include feelings of extreme sadness, hopelessness, suicidal ideation, anxiety, and fatigue, which mirror those of a major depressive episode with the additional criteria that the onset of depression occurs within 4 weeks of childbirth. PPD can affect a mother's ability to care for her child and may negatively affect a child's cognitive development.[8]

Rapid changes in the levels of endogenous neurosteroids during pregnancy are thought to be related to the development of PPD. Plasma levels of allopregnanolone, which is a metabolite of progesterone and an endogenous gamma-aminobutyric acid (GABA) modulator, are known to increase throughout pregnancy and then precipitously drop after delivery.[10, 5] It is thought that these rapid hormonal changes are linked to triggering depression in women who are vulnerable to develop this condition. Serotonin Selective Reuptake Inhibitors (SSRIs) are known to increase allopregnanolone, and it has been suggested that this mechanism could explain why SSRIs have shown therapeutic effect in the treatment of PPD.[6] However, there have been a limited number of placebo-controlled randomized clinical trials testing the efficacy of SSRIs, or any other medication, in the treatment of PPD.[15, 6]

Data were recently published that demonstrated that a continuous infusion of allopregnanolone rapidly alleviates symptoms of depression in women with PPD.[7] In this open-label study, 4 women with severe PPD received a 60-hour infusion of allopregnanolone. The mean Hamilton Depression Rating Scale for Depression (HAMD) before the infusion was 26.5 indicating that the women were severely depressed. Mean HAMD total score showed robust reductions even at the earliest time point measured (Mean HAMD 4.8 at Hour 12) and remained substantially lower through the end of infusion (Mean HAMD 3.3 at Hour 24, 1.8 at Hour 36, 2.3 at Hour 48, and 1.8 at Hour 60). Other end points showed similar improvements.

1.2 Product Background and Clinical Information

Ganaxolone is the 3β-methylated synthetic analog of the progesterone metabolite allopregnanolone. Allopregnanolone exhibits potent anxiolytic, antidepressant, antiepileptic, and sedative activity by virtue of its $GABA_A$ receptor modulating properties. As with allopregnanolone, ganaxolone potentiation of the $GABA_A$ receptor occurs at a site distinct from the benzodiazepine site. However, unlike allopregnanolone, ganaxolone cannot be converted to a hormonally active steroid.[1] Ganaxolone is currently under study for treatment of chronic neurologic and neuropsychiatric conditions such as epilepsy and behavioral problems associated with Fragile X Syndrome.

1.2.1 Ganaxolone Summary of Safety

As of October 10, 2017, 1557 unique subjects have received ganaxolone ranging in duration from 1 day to more than 2 years using doses from 50 to 2000 mg/day in completed studies. Of these subjects, 1527 subjects received oral ganaxolone and 30 subjects received IV ganaxolone.

In 20 completed Phase 1 studies, 319 healthy subjects received GNX oral doses of 50 to 2,000 mg/day for periods of up to 2 weeks or IV bolus doses ranging from 10 to 30 mg over durations of 2 minutes to 1 hour or a bolus dose of 6 mg over 5 minutes followed with a continuous infusion of 20 mg per hour for 4 hours.

In the 20 completed Phase 2/3 clinical studies, 1238 unique subjects have received oral ganaxolone in studies of adult subjects with epilepsy, pediatric subjects with seizure disorders, pediatric subjects with FXS, adult subjects with PTSD, and adult subjects with migraine.

1.2.1.1 Summary of Adverse Events

In clinical trials of ganaxolone, adverse events (AEs) related to the GABAergic mechanism of action in the CNS were reported more commonly in subjects receiving ganaxolone than placebo. In general, the frequency of these events has been dose related. Most of these effects were reported as mild or moderate and were reversible after dose decrease or drug discontinuation.

In all completed placebo-controlled studies, 61.7% (613/993) of subjects who received ganaxolone and 51.8% (330/637) of subjects who received placebo experienced at least 1 treatment emergent adverse event (TEAE). In these studies, the most frequently reported (i.e., in ≥5% of subjects) TEAEs in ganaxolone-treated subjects were CNS-related: somnolence (22.0% ganaxolone, 6.4% placebo), dizziness (13.0% ganaxolone, 4.2% placebo), fatigue (9.7% ganaxolone, 5.2% placebo), and headache (5.5% ganaxolone, 7.7% placebo). All of these events, except headache, occurred more frequently in ganaxolone-treated subjects than placebo subjects.

In placebo-controlled studies adverse event of rash led to discontinuations in GNX-treated subjects in 6 cases (6/993; 0.6%) compared to no cases (0/637; 0%) in placebo-treated subjects. One of the events was also reported as an SAE. In addition, in the ongoing study 1042-0900, an additional event of rash was reported as an SAE. Both SAEs resolved after discontinuation of the study drug. There have been no cases of Stevens-Johnson syndrome, toxic epidermal necrolysis or any other clinically important rashes reported in the clinical development program. Marinus considers rash as a potential rare adverse event associated with GNX.

1.2.1.2 Summary of safety of IV ganaxolone

Preclinical studies and a study in 36 healthy volunteers assessing safety, pharmacokinetics and pharmacodynamics of intravenously administered ganaxolone has been completed. Preclinical toxicity studies showed intravenous (IV) ganaxolone to be generally safe and adverse events consistent with expected dose-related sedation. In rats continuously dosed with IV ganaxolone for 14 days no ganaxolone-related changes were noted in clinical pathology parameters or histopathology examination. There was no evidence of local irritation when ganaxolone was given intra- or perivenously in preclinical studies. Furthermore, IV ganaxolone did not cause hemolysis and was compatible with human plasma.

The safety, pharmacokinetics and pharmacodynamics of IV ganaxolone were investigated in healthy 36 volunteers in Study 1042-0405, in which ganaxolone was administered as a bolus dosing (Stage 1) or as a bolus dose followed by a continuous infusion (Stage 2). Ten of the 36 subjects enrolled were women.

- Stage 1 enrolled and dosed subjects in 4 cohorts (A-D): 6 subjects in Cohort A (10 mg ganaxolone IV bolus in 3 subjects and 30 mg ganaxolone bolus in 3 subjects over 5-minutes), 8 subjects in Cohort B (20 mg ganaxolone bolus over 2-minutes), 8 subjects in Cohort C (30 mg ganaxolone bolus over 1-hour) and 8 subjects in Cohort D (10 mg ganaxolone bolus over 1-hour). Cohorts B, C and D included 2 placebo subjects in each cohort.
- Stage 2 of the study dosed a total of 6 subjects with a 6 mg bolus followed by a 4-hour infusion at 20 mg/h. Ten of the 36 subjects enrolled in Study 1042-0405 were women.

A total of 35 of the 36 subjects enrolled in Stages 1 and 2 completed the study as planned while 1 subject withdrew their consent.

Six subjects reported treatment emergent AEs in Stage 1 and 2. No single AE was seen twice. Only one event, headache, was considered by the investigator to be related to ganaxolone. None of the treatment emergent AEs was serious, and all were of mild intensity. No clinically meaningful mean changes in laboratory test results, vital signs, or ECG parameters occurred in any cohort.

Pharmacokinetic data from Study 1042-0405 showed that a bolus infusion of 30 mg ganaxolone over 5-minutes led to peak concentration levels (Cmax) of > 1,000 ng/ml with no safety concerns (except sedation). Infusion of 30 mg/h for 1 hour, 20 mg over 2 minutes and 20 mg/h for 4 hours led to peak concentrations of 258 ng/mL, 441 ng/mL and 215 ng/mL, respectively, again without any safety concerns. This is consistent with findings from previous studies with the oral formulation of ganaxolone, in which Cmax levels of up to 200 to 300 ng/mL were commonly observed and were not associated with major safety findings or toxicity (apart from sedation-related effects).

1.2.1.3 Other ganaxolone safety information

Ganaxolone is metabolized by CYP3A4/5, and *in vitro* data and human PK data from subjects taking strong CYP inducers (carbamazepine and phenytoin) has shown increased ganaxolone clearance with approximately a 45% lowering in overall ganaxolone levels and exposure. Marinus considers interaction with strong inducers and inhibitors as a potential risk associated with the use of ganaxolone.

In the ganaxolone development program overall, no clinically significant trends in electrocardiogram (ECG) intervals, vital signs, or physical or neurological examinations have been noted, and no mean changes from baseline in clinical laboratory results have been identified. In the completed placebo-controlled Phase 1, 2, and 3studies, 0.32% of subjects who received GNX and 0.46% of subjects who received placebo developed elevated LFTs during the study (>3x ULN AST and/or ALT). A subject participating in the ganaxolone pediatric epilepsy study 1042-0900 developed liver failure, which was not considered to be related to ganaxolone. The subject was diagnosed with short bowel syndrome, liver steatosis and IgG-cholangitis, which were considered to be the causal factors for the subject's liver failure. There have been no other cases of Hy's Law or liver failure in the ganaxolone development program.

It is not known if ganaxolone is excreted to breast milk. After cessation of the dosing, plasma ganaxolone levels are expected to drop rapidly, but it is possible that low sub-therapeutic levels persist for several days as ganaxolone is slowly released from tissues. Therefore, a washout period of 45 days is required following cessation of ganaxolone treatment before breast-feeding. Previous toxicology studies in animals focusing on prenatal and neonatal development have not demonstrated toxicities associated with ganaxolone. Ganaxolone has been administered to infants with severe forms of epilepsy as early as 4 months of age.

In clinical trials involving administration of ganaxolone over several weeks, the study drug has been tapered off over a 1 to 2-week period. There have been no reports of withdrawal symptoms emerging after cessation of ganaxolone.

1.2.1.4 Preliminary safety information from the current trial (1042-PPD-2002)

Cohort 1

Dosing for the Cohort 1 of this study has been completed. In this cohort ganaxolone was infused at a rate of 4 mg/h for 48 hours after which the rate was lowered to 2 mg/h for the next 12 hours. The infusion was stopped at 60 hours. [redacted]. There were no serious adverse events or adverse events leading to discontinuation, and no subject needed a dose adjustment. The DRC deemed the Cohort 1 dose to be well-tolerated and recommended increasing the dose from 4 mg/h (Cohort 1) to 8 mg/h for Cohort 2.

Cohort 2

[redacted]. In this cohort ganaxolone was infused at a rate of 8 mg/h for 48 hours after which the rate was lowered to 4 mg/h for the next 12 hours. The infusion was stopped at 60 hours. There have been no serious adverse events or adverse events leading to discontinuation, and no subject has needed a dose adjustment. The DRC has evaluated preliminary adverse event data from these 12 subjects and deemed this dosing regimen to be well-tolerated. The DRC has recommended increasing the dose to 12 mg/h for Cohort 3.

Cohort 3

[redacted] and respective data reviewed by the DRC. In this cohort ganaxolone (or matching placebo) was given as 12 mg IV bolus over 2 minutes followed by IV infusion at a rate of 12 mg/h for 48 hours after which the rate was lowered to 6 mg/h for the final 12 hours. The infusion was stopped at 60 hours. There have been no serious adverse events or adverse events leading to discontinuation, and no subject has needed a dose adjustment. The DRC has evaluated preliminary adverse event data from these 13 subjects and deemed this dosing regimen to be well-tolerated. The DRC has recommended that enrollment into Cohort 3 be completed with 20 subjects.

2.0 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Rapidly declining plasma levels of allopregnanolone and other neurosteroids, after childbirth are thought to be linked to triggering depression in women who are vulnerable to development of this condition. Ganaxolone, a synthetic analog of allopregnanolone, may provide benefit to these women.

This study will explore whether ganaxolone is safe and well tolerated in women suffering from PPD. In addition, ganaxolone's efficacy in treating depressive symptoms will be assessed through a set of exploratory analyses. Plasma levels of ganaxolone will be determined through pharmacokinetic analysis. The study results will be used to select a ganaxolone dose and dosing regimen for further development in PPD.

2.2 Study Objectives

2.2.1 Safety Objective

To assess the safety and tolerability of escalating doses of IV ganaxolone as determined by AEs and changes from baseline in laboratory measures, vital signs, Columbia Suicide Severity Rating Scale (CSSRS), electrocardiogram (ECG), Stanford Sleepiness Scale (SSS), and physical examination. In Cohort 6 the safety of IV dosing followed by oral dosing is investigated using the same assessments as in Cohorts 1-5.

2.2.2 Efficacy Objective

To explore the efficacy of escalating doses of IV ganaxolone in the treatment of PPD with the 17-item Hamilton Depression Rating Scale (HAMD17), Edinburgh Postnatal Depression Scale (EPDS), Spielberger State-Trait Anxiety Inventory six item version (STAI6) and Clinical Global Impression-Improvement (CGI-I) scale. In Cohort 6 the efficacy of IV dosing followed by oral dosing is explored using the same assessments as in Cohorts 1-5.

2.2.3 Pharmacokinetic Objective

To collect samples of blood for pharmacokinetic analysis to assess ganaxolone plasma exposure after administration of intravenous and oral ganaxolone.

3.0 STUDY DESIGN

3.1 Study Design and Study Population

This is a Phase 2A, double-blind, placebo-controlled, multiple-dose escalation study consisting of up to 6 cohorts (Cohorts 1-6).

Approximately 200 women with PPD 18–45 years of age will be screened to randomize up to 100 subjects across up to 6 cohorts. Approximately 10-30 subjects will be randomized into each cohort.

In Cohorts 1-5, the treatment is administered intravenously over 60 hours. Randomized subjects will receive IV ganaxolone or matching IV placebo in a 1:1 ratio. More specifically, the dosing for Cohorts 1-5 is as follows:

Cohort 1: ganaxolone is infused at a rate of 4 mg/h (16 ml/h of ganaxolone 0.25 mg/ml solution) for 48 hours and then at a rate of 2 mg/h for the next 12 hours. The infusion is stopped at 60 hours.

Cohort 2: ganaxolone is infused at a rate of 8 mg/h (16 ml/h of ganaxolone 0.5 mg/ml solution) for 48 hours and then at a rate of 4 mg/h for the next 12 hours. The infusion is stopped at 60 hours.

Cohort 3: Twelve mg bolus of ganaxolone is initially given over 2 minutes followed by ganaxolone infusion at a rate of 12 mg/h (24 ml/h of ganaxolone 0.5 mg/ml solution) for 48 hours. The rate is then reduced to 6 mg/h for the next 12 hours. The infusion is stopped at 60 hours.

Cohorts 4 and 5: Cohorts 4 and 5 are optional and will be utilized only if further dose exploration is warranted. Ganaxolone infusion rate will be decided based on the results of Cohorts 1-3. However, the initial bolus dose will not exceed 16 mg over 2 minutes and the maximum infusion rate will not exceed 16 mg/h.

In Cohort 6, subjects randomized to ganaxolone will receive an initial IV infusion of 20 mg/h (40 ml/h of ganaxolone 0.5 mg/ml solution) for 6 hours followed by 900 mg (4 capsules) ganaxolone capsules administered orally at dinner time for 28 days followed by a 3-day taper (3, 2, and 1 capsules per day, respectively). Subjects randomized to placebo will receive an initial IV infusion of matching placebo (at 40 ml/h) followed by 4 placebo capsules administered orally at dinner time for 28 days followed by a 3-day taper (3, 2, and 1 capsules per day, respectively). Randomization will allocate subjects to the ganaxolone arm or placebo arm in 1:1 ratio.

3.2 Rationale for Study Design

Rapid changes in allopregnanolone and other neurosteroid levels during and after pregnancy are thought to contribute to the biological underpinnings of PPD. There are also data suggesting that

the sensitivity of the GABA system is altered during pregnancy and after childbirth, possibly as a result of changes in the circulating neurosteroid levels, and that there may be a state of neurosteroid withdrawal after pregnancy.[11] Ganaxolone may alleviate PPD by increasing neurosteroid activity.

Although ganaxolone has been administered to more than 1,500 subjects there have been no prior studies establishing the safety or efficacy of ganaxolone in clinical studies of PPD or other mood disorders in women. This study is designed to establish the safety profile of intravenous ganaxolone in women with PPD. The safety of transition from IV treatment to oral treatment is investigated in Cohort 6. Potential efficacy signals will also be explored. These data will be used to select a dose (or doses) and dosing regimen for further development of ganaxolone in PPD.

3.3 Blinding Scheme

Within cohorts, subjects will be randomized to ganaxolone or placebo in a 1:1 ratio. The randomization scheme will be prepared by an independent third-party vendor. Treatment assignments will be obtained by the investigator (or designee) via an Interactive Voice and/or Web Response System (IxRS). Subjects who are randomized to receive ganaxolone in Cohorts 1-5 will receive ganaxolone as an intravenous infusion for 60 hours with or without an intravenous ganaxolone bolus dose. Subjects who are randomized to placebo will receive matching placebo infusion for 60 hours (0.9% saline) with or without a matching intravenous placebo bolus dose. The placebo infusion is identical to ganaxolone in its appearance. In Cohort 6, subjects randomized to ganaxolone will receive an initial infusion of 20 mg/h (40 ml/h of ganaxolone 0.5 mg/ml solution) for 6 hours followed by treatment with oral doses of 900 mg ganaxolone (4 capsules per dose) for 28 days followed by a 3-day taper (3, 2, and 1 capsules per day, respectively). Subjects randomized to placebo will receive an initial infusion with matching IV placebo (at 40 ml/hr) followed by matching oral placebo (4 capsules per dose) for 28 days followed by a 3-day taper (3, 2, and 1 capsules per day, respectively). The placebo infusion and placebo capsules are identical to the ganaxolone infusion and ganaxolone capsules, respectively, in their appearance. An unblinded study pharmacist at the investigative site will prepare the ganaxolone and placebo IV solutions and allocate capsule supply for Cohort 6. Members of the DRC will be unblinded at scheduled DRC meetings. All other study personnel, including persons involved in the evaluation of the study subjects (e.g. investigators, sub-investigators, and physicians/nurses), will remain blinded at all times, except in case of an emergency. Subjects will be blinded.

3.4 Dose Selection

3.4.1 Cohort 1

For Cohort 1, the targeted ganaxolone plasma concentration at steady state (C_{ss}) will be 52 ng/ml, which is estimated to be achieved with a ganaxolone infusion rate of 4 mg/hr (16 ml/h of ganaxolone 0.25 mg/ml solution). Steady state is expected to be achieved within 24 hours.

For Cohort 1, the infusion rate is lowered to 2 mg/h after + 48 hours of infusion and stopped at + 60 hours. This is done to minimize any risks for withdrawal or rebound of anxiety and depression symptoms.

The target ganaxolone exposure level of approximately 52 ng/ml for Cohort 1 was chosen to achieve a level similar to that of allopregnanolone at the end of pregnancy. Allopregnanolone levels increase gradually throughout pregnancy reaching a peak mean concentration at the end of pregnancy of about 15 to 60 ng/ml. The levels then drop precipitously after the delivery.[10, 5, 14] We hypothesize that substitution of the low allopregnanolone levels with ganaxolone would alleviate or reverse the symptoms of PPD.

3.4.2 **Cohort 2**

For Cohort 2, the ganaxolone infusion rate will be 8 mg/hr (16 ml/h of ganaxolone 0.5 mg/ml solution). The infusion rate will be lowered to 4 mg/h (8 ml/h of ganaxolone 0.5 mg/ml solution) after + 48 hours of infusion and will be stopped at + 60 hours. This is done to minimize any risks for withdrawal or rebound of anxiety and depression symptoms. This dose will approximately double the expected plasma exposure as compared to Cohort 1 at steady state (Cohort 2 expected plasma concentration ~ 100-120 ng/mL).

3.4.3 **Cohort 3**

For Cohort 3, an initial 12 mg bolus of ganaxolone will be given over 2 minutes, followed by ganaxolone infusion at a rate of 12 mg/h (24 ml/h of ganaxolone 0.5 mg/ml solution) for 48 hours. The rate will be reduced to 6 mg/h for the next 12 hours, which is done to minimize any risks for withdrawal or rebound of anxiety and depression symptoms. The infusion is stopped at 60 hours.

This dose will increase the expected maximum plasma exposure by about 1.5-fold as compared to Cohort 2 at steady state during the infusion. The expected maximum plasma concentrations will be ~ 180 ng/ml during the infusion. During the initial 2-minute ganaxolone bolus, the peak plasma concentrations are expected to increase up to 300 ng/ml transiently, and then falling rapidly below 100 ng/ml after the bolus dose has been completed.

The bolus dose is justified to provide a rapid loading dose of ganaxolone, which is hypothesized to expedite the onset of antidepressant activity.

Based on prior studies with the oral formulation and results from Phase 1 Study 1042-0405 in healthy volunteers using the IV formulation of ganaxolone, the Cohort 3 dose and associated plasma exposure is expected to be generally safe and well tolerated.

3.4.4 **Cohorts 4 and 5**

Cohorts 4 and 5 are optional and will be utilized only if further dose exploration is warranted. Ganaxolone infusion rate will be decided based on the results from previous cohorts. However, no bolus doses higher than 16 mg over 2 minutes will be administered. The cap for the maximum infusion rate in Cohorts 4 and 5 will be 16 mg/h (not including any ganaxolone given by bolus). Ganaxolone was administered to healthy volunteers in Study 1042-0405 at these dose levels and above without any safety concerns (see below for details). With this maximum bolus and infusion rate the amount of Captisol® infused over 24 hours will not exceed the maximum levels achieved with Carnexiv®, an approved IV carbamazepine product.

3.4.5 **Cohort 6**

For Cohort 6, the goal of initiation of treatment with IV infusion followed by oral capsules is to maximize the speed of onset of antidepressant activity while providing the convenience of oral dosing for the remainder of the treatment period. Under this IV-oral dosing schedule there may not be a need for a prolonged inpatient observation.

This initial infusion is targeted to provide a fast onset of antidepressant activity by delivery of rapid plasma exposures to ganaxolone. At dinner time of Day 1 the subjects will take their first oral dose of ganaxolone 900 mg or matching placebo (4 capsules). This dose is expected to provide mean C_{max} plasma concentrations of approximately 250-300 ng/mL and mean steady-state levels between 90 and 150 ng/mL, which may be mildly sedating. In previous studies ganaxolone has been given up to a daily dose of 2000 mg, and at single doses of 1000 mg. Based on the previous experience this dose is expected to be safe.

At subsequent nights (Days 2-28), the target dose is ganaxolone 900 mg or matching placebo (4 capsules) at dinner time followed by a 3-day taper (3, 2, and 1 capsule/s per day, respectively). However, based on the assessment of the investigator the dose may be maintained at 675 mg or 450 mg (or matching placebo) in case of adverse events, such as grogginess in the morning. In the case of 3 capsules per day on day 28 the taper will consist of 2, 2, and 1 capsule/s on days 29, 30, and 31, respectively. In the case of 2 capsules per day on day 28 the taper will consist of 1 capsule on days 29, 30, and 31. If the subject cannot tolerate 450 mg (or matching placebo) per dose the investigator will contact the Medical Monitor to discuss dosing options.

Subjects will be provided with a diary to capture the details of dose administration and associated food intake throughout the treatment period. Subjects will document the number of capsules taken and whether a fatty meal/snack (e.g., fatty yogurt, nuts, avocado) was consumed ±15 minutes of taking the capsules.

The mechanism by which ganaxolone is postulated to be efficacious under this dosing regimen is restructuring of sleep architecture.[2] Preclinical studies have shown that allopregnanolone has the capacity to modulate sleep, and disturbed sleep architecture is one of the hallmarks of depression.

3.4.6 **Dose justification in context of previous experience with IV ganaxolone**

In Study 1042-0405, which was a Phase 1 study in healthy volunteers investigating the safety of IV ganaxolone, infusion of 30 mg/h for 1 hour, 20 mg over 2 minutes and 20 mg/h for 4 hours led to peak concentrations of 258, 441 and 215 ng/mL, respectively, without any safety concerns. Sedation was assessed using the Modified Observers Assessment of Alertness/Sedation (MOAAS) scale. On this scale, score 5 indicates no sedation (responds readily to name spoken in normal tone) while score 1 indicates deep sedation (responds only after painful trapezius squeeze). In these cohorts, vast majority of the scores were 5 with few exceptions of 4 (lethargic response to name spoken in normal tone) and 3 (responds only after name is called loudly or repeatedly). The sedation scores reversed quickly after the infusion was stopped. The highest bolus dose tested was 30 mg, which was infused over 5-minutes. This dose led to peak concentration levels (C_{max}) of > 1,000 ng/mL with no safety concerns (except sedation).

Six subjects reported treatment emergent AEs. No single AE was seen twice. Only one event, headache, was considered by the investigator to be related to ganaxolone. None of the treatment emergent AEs was serious, and all were of mild intensity. No clinically meaningful mean changes in laboratory test results, vital signs, or ECG parameters occurred in any cohort.

This safety profile is consistent with findings from previous studies with the oral formulation of ganaxolone, in which C_{max} levels of up to 200 to 300 ng/mL were commonly observed and were not associated with major safety findings or toxicity (apart from sedation-related effects).

3.5 Justification for Placebo as a Control Group

There are no approved treatments for PPD although SSRIs and serotonin and norepinephrine reuptake inhibitors (SNRIs) are commonly used off-label to manage PPD. All subjects whether randomized to the placebo or control group will be allowed to remain on their current antidepressants provided that they have not had a recent change in the medication regimen (for details, please see Section 5.3.2 for prohibited treatments). The add-on design minimizes subject risks because the current medications are not withdrawn, since that could exacerbate depressive symptoms. The duration of the double-blind treatment phase in Cohorts 1-5 of the study is short (60 hours) and is conducted in an inpatient setting, which further minimizes risks to the subjects. The Cohort 6 treatment period is initiated in an inpatient setting, which allows observation of the effects of the IV infusion and first dose effects of the oral medication during the approximately 48-hour stay on the unit.

3.6 Study Duration

The screening period for each cohort will be up to 2 weeks. In Cohorts 1-5 the screening period is followed by a 60-hour infusion treatment with or without initial bolus dosing during the 4-day inpatient treatment phase at a hospital or clinical pharmacology unit. The subjects will be discharged from the unit on the morning of Day-4. There will be 2 safety follow-up visits after inpatient discharge on post-treatment Weeks 1 and 4. The total duration of the study will be up to 7 weeks for Cohorts 1-5. For Cohort 6 there will be an initial infusion treatment and oral dose during the approximately 24-hour inpatient dosing phase followed by 27 days of oral treatment as outpatient. There will be 3 safety follow-up visits after the outpatient treatment period on post-treatment Weeks 1,4, and 6. The total duration of the study will be up to 12 weeks for subjects participating in Cohort 6.

3.7 Interim Analyses

The study team physician and the clinical operations lead will monitor emerging **blinded** safety data from each subject periodically throughout the duration of the study.

In addition, safety and efficacy data from each cohort will be unblinded, and analyses will be conducted for the purpose of dose selection for the next cohort. The dose for the next cohort will be decided based on these interim data analyses. The decision how to adjust the dose and/or the duration of the infusion will be made based on recommendations by a Data Review Committee (DRC) composed of the sponsor's Chief Medical Officer, and at least 2 other external physicians. At least one of the members will have special expertise in the clinical care of women with depression or postpartum depression. One of the members will have expertise in the

conduct of clinical trials or analysis of clinical trial data. The study team and all parties other than the DRC will remain blinded.

The dose for the subsequent cohorts will be selected with the goal of gaining additional information on ganaxolone's tolerability and dose-response profile.

A separate DRC guidance document outlines the principles for dose selection. Marinus may decide to stop the study, or make the data public, after completion of any cohort.

3.8 Definition of Completion

A cohort is considered complete when the final subject in the cohort has completed the final protocol-defined assessment, including follow-up visits, for the cohort.

The Study Completion Date is defined as the date the final subject, across all sites, completes her final protocol-defined assessment, including follow-up visits, for the final cohort.

3.9 Sites and Regions

The study will be conducted in the United States at approximately 20 investigative sites.

4.0 STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

1. An understanding of and ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
3. Female aged 18 to 45 years, inclusive, at the Screening Visit
4. Experiencing a Major Depressive Episode, which started between the start of the third trimester and 4 weeks following delivery. The Major Depressive Episode must be diagnosed according to MINI 7.0 interview
5. Given birth in the last 12 months
6. HAMD17 score of ≥ 26 at screening (HAMD17 must be ≥ 22 per CTNI rating at Admission to the Unit on Day 0)
7. The diagnosis of PPD and severity of depression must be supported by the SAFER interview
8. Must agree to stop breastfeeding from start of study treatment to 45 days after end of study treatment
9. Must agree to use acceptable contraceptive methods during the study period

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Current or past history of any psychotic illness, including Major Depressive Episode with psychotic features
2. Any psychiatric condition that, in the investigator's judgment, is considered clinically significant and could affect subject safety or study outcome including eating disorder, panic disorder, obsessive-compulsive disorder, or post-traumatic stress disorder
3. History of suicide attempt within the past 3 years (actual attempt, interrupted or aborted attempt, preparatory acts, or behavior)
4. Active suicidal ideation (e.g. answering "yes" to questions 4 or 5 in the CSSRS suicidal ideation section)
5. History of severe bipolar I disorder (e.g. hospitalization due to the illness, lifetime history of psychosis or suicide attempt)

6. Uncontrolled seizure disorder
7. Current or history within the past 3 years of any substance use disorder, with the exception of tobacco or caffeine
8. Positive drug screen for any illicit substances or prescription drugs at screening or randomization. If the drug screen is positive for a prescription drug that has the potential to be abused (e.g. amphetamine, benzodiazepine), legitimate use of the drug must be verified by the subject's providing the current pill bottle, prescription for the drug, or a note from the prescribing physician. Cannabis use is prohibited and subjects with positive drug screen for cannabis are excluded. However, occasional users of cannabis may be re-tested if the subject is willing to refrain from consuming cannabis-based products during the trial. If the re-test sample is negative at screening the subject can be considered eligible. If the re-test sample is positive for cannabis the investigator may ask for determination of the urine or blood levels of Δ9-tetrahydrocannabinol (THC), and its metabolites 11-hydroxy-THC and, 9-carboxy-THC. If the levels of THC are not detectable the subject may be considered eligible for the trial.
9. Current or relevant history of any medical disorder that may require treatment or make the subject unlikely to be able to complete the study, or any condition that presents undue risk from the investigational product or procedure point of view
10. Any clinically significant abnormality identified on physical examination, ECG or laboratory tests, that in the judgment of the investigator would compromise the subject's safety or successful participation in the clinical study
11. Subject has untreated or uncontrolled hypothyroidism
12. Known or suspected intolerance or hypersensitivity to the investigational product(s) or allopregnanolone, or any of the stated ingredients
13. Use of another investigational product within 60 days prior to the first dose of investigational product
14. Has alanine transferase (ALT) or aspartate transferase (AST) greater than 2.5 times upper limit of normal or total bilirubin greater than 1.5 times upper limit of normal (unless elevation is due to Gilbert's syndrome)
15. Screening QTcF > 470 msec
16. Unwillingness to withhold grapefruit, Seville oranges, star fruit, or citrus derived products from diet between screening and discharge from the study unit
17. Receiving concomitant treatment with strong CYP3A4 inducers or strong CYP3A4 inhibitors
18. Body mass index (BMI) ≥ 40
19. Subject is pregnant
20. Subject is using prohibited medications as specified in Section 5.3.2

4.3 Reproductive Potential

4.3.1 Female Contraception

Sexually active females of childbearing potential should be using an acceptable form of contraception throughout the study period between screening and last follow-up visit.

Acceptable methods of contraception are:

- Intrauterine device plus condoms (If the subject has a hormone-releasing intrauterine device (IUD) this must have been in place for a minimum of 30 days)
- Double-barrier methods (e.g. condoms with spermicidal gel, foam or sponge, diaphragm with spermicidal gel, foam or sponge)
- Hysterectomy or tubal ligation at or after delivery

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g. in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from the investigational product with the medical monitor when possible. Withdrawn subjects who have not received IP will be replaced.

If the investigational product is discontinued, regardless of the reason, the evaluations listed for Day 4 are to be performed as completely as possible for Cohort 1-5, and Day 28 evaluations for Cohort 6. Whenever possible, all discontinued subjects should also undergo the protocol-specified follow-up. Comments (spontaneous or elicited), complaints or AEs reported by the subject must be recorded in the source documents. The reason for discontinuation and the date and time of discontinuation of the investigational product must be recorded in the case report form (eCRF) and source documents.

4.4.1 Subject Withdrawal Criteria

All subjects reserve the right to withdraw from the clinical study at any time, as stated in the informed consent form (ICF). The Investigator may discontinue subjects from the clinical study for any of the following reasons:

1. ECG evidence of QT prolongation (QTcF > 530 msec, or an increase of QTcF > 60 msec above baseline to a value > 480 msec on the 12-lead ECG, confirmed on a repeat 12-lead ECG taken after resting at least 5 minutes in a supine or semi-recumbent position after the original finding of prolonged QTcF).
2. It is the Investigator's opinion that it is not in the subject's best interest to continue in the study.
3. Any subject who exhibits any Suicidal Behavior or Suicidal Ideation (e.g. subject answers "yes" to question 4 or 5 in the Suicidal Ideation section of the CSSRS). These subjects should be evaluated by a psychiatrist immediately.

4. Rash that is clinically significant and considered to be related to the study drug (e.g. morbiliform, urticarial, papular).
5. Subject experiences an SAE considered to be related to the study drug

4.4.2 **Decisions to discontinue the study will be made at each participating site by the Principal Investigator. If feasible, the reason for discontinuation should be discussed with the Medical Monitor. Reasons for Discontinuation**

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

Reasons for discontinuation include but are not limited to:

- AE
- Protocol deviation
- Withdrawal of consent by subject
- Lost to follow-up
- Lack of efficacy
- Other (If "Other" is selected, the investigator must specify the reason on the eCRF)

4.4.3 **Subjects "Lost to Follow-up" Prior to Last Scheduled Visit**

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that she return to the site for final safety evaluations. If a contact is made but the subject refuses or is unable to come to the final safety evaluation it should be documented in the eCRF.

5.0 PRIOR AND CONCOMITANT TREATMENT

All non-study treatments (including herbal treatments, vitamins, and non-pharmacological treatments) received within 60 days prior to the screening visit (Visit 1) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate eCRF page.

5.1 Prior Pharmacological Treatment

Prior pharmacological treatment includes all treatments (including herbal treatments and vitamins) that the subject received and stopped within 60 days of the date of the screening visit. For example, if the subject had been treated with sertraline during pregnancy but it was discontinued 3 weeks prior to the screening visit, this medication would be recorded on the prior medication eCRF page.

5.2 Concomitant Pharmacological Treatment

Concomitant treatment refers to all treatments (including herbal treatment and vitamins) taken between the screening visit and the end of the follow-up period regardless of the start date of the concomitant medication. For example, if the subject was started on a prenatal vitamin and it was continued through the study period, this treatment would be recorded on the concomitant medication eCRF page.

5.3 Concomitant Psychological Treatment

Concomitant psychological treatment refers to all psychological care the subject is receiving between the screening visit and the end of the follow-up period regardless of the start date of the concomitant psychological treatment. Concomitant psychological treatment information must be recorded on the concomitant psychological treatments eCRF page.

5.3.1 **Permitted Treatment**

5.3.1.1 Permitted Psychological Treatments

The subject may continue their current form of psychological treatment (e.g. Cognitive Behavioral Therapy, Psychodynamic Psychotherapy, Supportive Psychotherapy) throughout the treatment period. However, initiation of a new therapy (a new treatment modality or switching a therapist) is prohibited between screening and discharge from the inpatient unit.

5.3.1.2 Permitted Antidepressant Treatments

The subject may continue their current SSRI, SNRI or bupropion or other serotonin or norepinephrine modulating antidepressant (e.g. vortioxetine, mirtazapine) treatment provided the regimen conforms to the standard of care and the medication was started at least 21 days before the screening visit, and there has not been a dose change within 7 days of the screening visit. The antidepressant medication must have been approved for treatment of major depressive

disorder by the United States (US) Food and Drug Administration (FDA). Monoamine Inhibitors are prohibited (including all formulations of selegiline). Tricyclic antidepressant medications will be decided on a case-by-case basis with the medical monitor.

5.3.1.3 Other Permitted Treatments

The subject may continue her current non-psychiatric medications with the exception of medications that are strong inducers or inhibitors of CYP3A4 (Appendix 1).

The subject may use diphenhydramine 25 to 50 mg, trazodone 25 to 50 mg or doxepin 3 to 5 mg during the inpatient or outpatient phase for severe insomnia as needed. Only 1 dose of 1 of the medications is allowed per night. It is recommended to use the same medication each night. To minimize carryover effects there should be a minimum of 10-hour interval between administration of an allowed hypnotic and any efficacy assessment. Other hypnotics, such as zolpidem or zaleplon, are prohibited.

If the subject is treated with an atypical antipsychotic medication that was started with the purpose of augmenting the therapeutic effect of an antidepressant (i.e. the antipsychotic is not intended for treatment of psychosis or mood stabilization), she may continue this treatment throughout the study period. Examples of such treatments would be quetiapine 50 mg at bedtime and aripiprazole 15 mg daily. However, the antipsychotic medication must have been started at least 21 days before the screening, and there should not have been a dose change within 7 days of screening.

Other medications and medication combinations should be discussed with the medical monitor before enrolling the subject in the study.

After the subject completes the study treatment period, any changes to the antidepressant or antianxiety medication regimen are not prohibited, but investigators are encouraged to maintain such drugs at stable doses if possible. Any changes in the medication regimen must be recorded on the concomitant medication eCRF page.

5.3.2 **Prohibited Treatments**

The following classes of medications and treatments are prohibited during the study treatment period. If the subject has been taking any of these medications before enrollment, there should be a medication-free period of a minimum of 5 days or 5 half-lives of that medication, whichever is longer, before admission to the unit. In general, subjects who require extensive washouts may not be candidates for participation and those cases should be discussed with the medical monitor.

- Benzodiazepines and barbiturates
- Gabapentin and pregabalin
- Anticonvulsants and mood stabilizers
- All hypnotics and sleep aids (with the exception of low-dose diphenhydramine, doxepin, and trazodone as described above)
- Opioids

- Cannabis
- Electroconvulsive Therapy (ECT), rapid transcranial magnetic stimulation (rTMS), vagal nerve stimulation
- Experimental (including hormonal and herbal) treatments of postpartum depression
- Strong inhibitors and inducers of CYP3A4 (Appendix 1)

6.0 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

6.1.1 Ganaxolone IV infusion solution

Manufacturer: Particle Sciences Inc.

Vehicle: Captisol® containing sterile IV solution

Formulation: IV

Strength: 3 mg/ml solution in a glass vial, which is to be diluted with 0.9% saline for the infusion. For details regarding preparation of the infusion solution please see pharmacy manual.

Route of administration: IV

6.1.2 Placebo IV control solution

Placebo name: 0.9% saline physiological sterile IV solution

Formulation: IV solution matching ganaxolone in appearance

Strength: not applicable

Route of administration: IV

6.1.3 Ganaxolone oral capsules

Ganaxolone capsules will be provided in size 00 white/opaque gelatin capsules packaged in HDPE bottles with a foil induction seal and child resistant closure. Each bottle will contain 70 capsules. Each capsule contains 225 mg ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one), and hydroxypropyl methylcellulose, sucrose, polyethylene glycol 3350, polyethylene glycol 400, sodium lauryl sulfate, sodium benzoate, citric acid anhydrous, sodium methyl paraben, microcrystalline cellulose, 30% Simethicone Emulsion, gelatin capsules, polysorbate 80, and sodium chloride.

6.1.4 Placebo oral capsules

Placebo formulation is comprised of sucrose spheres of comparable size to the ganaxolone spray layered spheres encapsulated in a size 00 white/opaque gelatin capsule. The weights of placebo capsules are matched to ganaxolone capsules. The placebo capsules will be provided to the sites in bottles identical to the active drug.

6.2 Administration of Investigational Product(s)

For administration of the IV investigational product (IP; ganaxolone or matching placebo [0.9% saline solution]) the investigator needs to use the Sponsor-approved Captisol®-compatible

intravenous infusion bags and infusion sets which are prepared according to the Pharmacy manual. Any substitutions and deviations from the Pharmacy manual need to be approved by the sponsor.

Ganaxolone or matching placebo capsules (Cohort 6 only) will be administered orally with food. Ganaxolone or matching placebo capsules should be taken ±15 minutes of a fatty meal or snack (e.g., fatty yogurt, nuts, avocado) and with 240 mL (8 oz) of water at dinner time.

Subjects will be provided with a diary to capture the details of dose administration and associated food intake throughout the treatment period. Subjects will document the number of capsules taken and whether a fatty meal/snack (e.g., fatty yogurt, nuts, avocado) was consumed ±15 minutes of taking the capsules.

6.2.1 Interactive Voice/Web Response System (IxRS) Technology for Investigational Product Management

The name and address of the Interactive Voice/Web Response System (IxRS) for this study will be maintained in the Investigator's files at each study site.

Interactive response technology will be used for the following investigational product tasks:

- Randomization
- Communication of treatment assignment to sites
- Supply management
- Inventory management and supply ordering
- Expiration date tracking
- Returns
- Emergency unblinding

6.2.2 Allocation of Subjects to IP

This is a double-blind, placebo-controlled study. The actual IP given to individual subjects is determined by a randomization schedule. prepared by an independent third-party vendor. Within cohorts, subjects will be randomized to ganaxolone or placebo in a 1:1 ratio

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to IP kit number allocated to the subject, once eligibility has been determined.

After being randomized a subject will be replaced only if she discontinues prior to receiving IP. The replacement subject will receive the same IP assignment as the replaced subject.

6.2.3 **Dosing**

Subjects entering the study will be randomized to ganaxolone or matching placebo at the Baseline Visit. The goal of Cohorts 1-6 is to determine safety, tolerability, PK and efficacy of the IV formulation (and in Cohort 6, the IV formulation followed by oral formulation) of ganaxolone in PPD subjects administered at a predicted dose regimen mimicking the levels of allopregnanolone at the end of pregnancy, or higher.[10, 5, 14]

Infusion rates for ganaxolone IV will be the same as for placebo IV. **Cohort 1**

The infusion rate for Cohort 1 will be 4 mg/h (16 ml/h of ganaxolone 0.25 mg/ml solution). The infusion rate (4 mg/ml or 16 ml/h) is maintained constant until + 48 hours when the rate is reduced to 2 mg/h and then stopped at + 60 hours.

The infusion rate of 4 mg/ml is estimated to produce a ganaxolone steady state level of about 52 ng/ml after about 24 hours of infusion.

Cohort 2

The infusion rate for Cohort 2 will be 8 mg/h (16 ml/h of ganaxolone 0.5 mg/ml solution). The infusion rate (8 mg/ml or 16 ml/h of ganaxolone 0.5 mg/ml solution) is maintained constant until + 48 hours when the rate is reduced to 4 mg/h (8 ml/h of ganaxolone 0.5 mg/ml solution) and then stopped at + 60 hours.

The infusion rate of 8 mg/h is estimated to produce a ganaxolone steady state level of about 100 ng/ml after about 24 hours of infusion.

Cohort 3

For Cohort 3, an initial 12 mg bolus of ganaxolone will be given over 2 minutes, followed by ganaxolone infusion administered at a rate of 12 mg/h (24 ml/h of ganaxolone 0.5 mg/ml solution) for 48 hours. The rate is then reduced to 6 mg/h for the next 12 hours. The infusion is stopped at 60 hours.

Cohort 4 and 5

Cohort 4 and 5 are optional and will be utilized only if further dose exploration is warranted. The dosing regimen for Cohort 4 and 5 will be decided based on the results of the Cohorts 1-3 and the recommendation of the DRC. However, no bolus doses higher than 16 mg over 2 minutes will be administered. The cap for the maximum infusion rate in Cohorts 4 and 5 will be 16 mg/h.

Cohort 6

For Cohort 6, an initial IV infusion 20 mg/h (40 ml/h of ganaxolone 0.5 mg/ml solution or matching placebo) for 6 hours will be followed by oral dose of 900 mg ganaxolone or matching placebo (4 capsules) at dinner time (Day 1). On subsequent nights (Day 2-28) the subject will take 900 mg of ganaxolone, or matching placebo (4 capsules), at dinner time followed by a 3-day

taper (3, 2, and 1 capsule/s per day, respectively (unless the dose is adjusted as per the instructions from the investigator in which case the taper follows instructions in section 3.4.6).

6.2.4 Dose Adjustments

Sedation and dizziness are known effects of ganaxolone at higher doses. If a subject experiences excessive sedation or dizziness the investigator may adjust the dosing by stopping the infusion for a minimum of 1 hour or until the effects resolve and then restarting the dosing at half the rate prescribed for the cohort (for Cohorts 1-5). For example, if the rate prescribed for the cohort is 4 mg/h (16 ml/h), the investigator may stop the infusion for 1 hour and then restart the infusion at 2 mg/h (8 ml/h). If the dose is adjusted, this must be recorded in the source documentation and eCRF. Under these circumstances the subject must be monitored closely for recurrence of sedation.

If the subject experiences excessive sedation or dizziness during the administration of the bolus dose, the dosing should be stopped immediately. The investigator should wait for a minimum of 1 hour or until the effects resolve and then starting the infusion at the rate prescribed for the cohort. Under these circumstances the subject must be monitored closely for recurrence of sedation. The dose of the oral medication in Cohort 6 may be adjusted by lowering the dose from 900 mg to 675 mg or 450 mg, or matching placebo at dinner time if the subject experiences adverse effects, such as sedation in the morning. If the dose is adjusted, this must be recorded in the eCRF. Other dosing adjustments may be possible, but they should be discussed with the medical monitor.

6.2.5 Blinding

The site pharmacy personnel who dispenses the study drug will not be blinded and will not be involved in any study assessments. All other participating staff involved in the evaluation and execution of the study will remain blinded to subject's study drug treatment.

6.2.6 Unblinding the Treatment Assignment

The treatment assignment must not be broken during the study except in emergency situations in which the identification of the investigational product is required for further treatment of the subject. The investigator should contact the medical monitor before unblinding, if possible. However, this should not delay unblinding in case of an emergency. The investigator should contact the medical monitor as soon as possible after the investigator has been unblinded.

In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the source documents. Upon breaking the blinding, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the Contract Research Organization (CRO) and sponsor.

6.3 Labeling, Packaging, Storage, and Handling

Further information regarding labeling, packaging, storage and handling can be found in the Pharmacy Manual.

6.3.1 Labeling

Each stock solution vial contains 88 mL of ganaxolone at a concentration of 3 mg/mL. A label is applied to each vial with information on strength, manufacturing batch number, manufacturing date, storage conditions, name of the manufacturer, and a warning that the drug is intended for research only.

The site pharmacy will prepare the IV bags, which will include at minimum the subject ID, protocol number, and time and date of IV bag preparation. No information which could potentially unblind the study drug should be visible to the subject or staff, and no packaging information should allude to the contents of the IV bag (e.g., "drug lot number"). Further details are provided in the pharmacy manual.

The Site Pharmacy will dispense the IV bag to a qualified blinded staff member who will administer the study drug to the subject.

For Cohort 6 the medication bottles (placebo and ganaxolone) will be labeled before shipping to the sites.

6.3.2 Packaging

6.3.2.1 IV ganaxolone

The sponsor will provide stock study drug solution which will be diluted by an unblinded research pharmacist at the investigative site. The sponsor will also provide or approve IV bags and empty syringes which are to be used for infusion and bolus dosing of the study drug and placebo. All packaging and labeling operations will be performed according to good manufacturing practice (GMP) and good clinical practice (GCP) guidelines. The study drugs will be prepared and supplied according to the randomization plan. Investigational products are prepared and distributed by the unblinded pharmacist. The pharmacist will enter the unique subject identifier on the investigational product as the product is distributed to the staff members managing administration of the study drug. Further details can be found in the pharmacy manual

6.3.2.2 Ganaxolone and placebo oral capsules

For Cohort 6 ganaxolone capsules and matching placebos will be provided in HDPE bottles.

All packaging and labeling operations will be performed according to good manufacturing practice (GMP) and good clinical practice (GCP) guidelines. Investigational products are prepared and distributed by the site pharmacist or delegated staff.

The site pharmacy or delegated site staff will be responsible for dispensing the study treatment to the subject. A sufficient number of capsules will be provided to the subject until the next study visit plus at least 3-day overage.

Detailed instructions when to take the medication and a reminder to take the study medication with fatty food (meal or snack, e.g., fatty yogurt, nuts, avocado) at dinner time and with 240 mL (8 oz) of water will be provided to the subject along with a medication diary to document intake of IP and fatty meal/snack ±15 minutes.

6.3.3 Storage

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacist, but this delegation must be documented.

The ganaxolone stock solution investigational product will be stored at refrigerated temperature 2ºC to 8ºC (36ºF to 46ºF).

The 0.3-micron ganaxolone capsules (225 mg) and matching placebos are stored in HDPE bottles with a foil induction seal and child resistant closure at room temperature (60^{o}F to 75^{o}F).

Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained. The temperature should be monitored continuously through use of either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. The sponsor or sponsor's delegate must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor or sponsor's delegate should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g. fumigation of a storage room.

6.4 Drug Accountability

Drug kits containing the study drug (ganaxolone stock vials for the IV solution, ganaxolone 225 mg capsules and matching placebo capsules) and supplies needed for each subject for the entire study will be supplied to the investigative site by the sponsor or a distributor on behalf of the sponsor. The pharmacist will inventory and acknowledge receipt of all shipments of the kits. The study drugs must be kept in a locked area with restricted access and stored and handled in accordance with the manufacturers' instructions. The pharmacist will also keep accurate records

of the quantities of study drug dispensed and used. The pharmacist is responsible for all drug supplies; written documentation is mandatory. The study monitor will periodically check the supplies of the study drug held by the pharmacist to verify accountability of all kits used. The pharmacist will dispense the kits according to the dosing plan. Upon receiving kits, the Principal Investigator and the team members will administer them only to the identified subjects in this study, following the procedures described in this study protocol and documented in the appropriate eCRF. At the conclusion of the study, all unused study drug will be returned or destroyed per the site's Standard Operating Procedures or instructions from the sponsor. The sponsor will verify that a final report of drug accountability to the unit-dose level is prepared and maintained in the Principal Investigator's study file.

6.5 Drug Administration

6.5.1 Administration of IV IP (Cohorts 1-6)

The IP will be administered IV via an indwelling catheter inserted in a vein on the arm or hand. The IP should be given as continuous infusion as instructed. If the study drug is stopped temporarily (e.g. catheter change) the infusion may be re-started at the same rate as before. A new infusion bag should be prepared every 24 hours. The catheter should be flushed with saline at the same time when the tubing is changed. The catheter site should be inspected for inflammation at least twice a day. For details please see pharmacy manual.

6.5.2 Administration of oral ganaxolone or placebo capsules (Cohort 6)

Oral doses of ganaxolone or matching placebo should be taken at dinner time with fatty food (±15 minutes of a fatty meal or snack, e.g., fatty yogurt, nuts, avocado) and with 240 mL (8 oz) of water at home.

Subjects participating in Cohort 6 will be informed about possible side effects from the study medication and cautioned to avoid quick postural changes. They should not carry the baby or sleep with the baby in the same bed due to the possible side-effect of dizziness and sedation. Subjects will be advised not to drive, operate heavy machinery, or participate in any potentially hazardous activity during the study that requires full mental alertness until they are sure the medication is not affecting alertness. They will also be cautioned that non-adherence to the dosing instructions (e.g. increasing the dose, taking the study medication doses too close together) could produce side effects.

The interaction between alcohol and ganaxolone is not known. Alcohol use is prohibited during the treatment period.

The subjects participating in Cohort 6 must have a reliable family member, significant other or a trusted friend who can take the role for being the primary childcare provider and a support person at home (including at nighttime) while the subject is participating in the trial.

7.0 STUDY PROCEDURES

This is a Phase 2A, double-blind, placebo-controlled, multiple-dose escalation study consisting of up to 6 cohorts. In Cohorts 1-5 the IV formulation of ganaxolone will be used while in Cohort 6 both IV and oral formulations will be used. Approximately 200 women with PPD 18 to 45 years of age will be screened to randomize approximately 100 subjects across the up to 6 cohorts. Approximately 10-30 subjects will be randomized into each cohort. Randomized subjects will receive ganaxolone or placebo in a 1:1 ratio. In Cohorts 1-5 the treatment is administered intravenously (with or without an initial bolus) over 60 hours. In Cohort 6 the treatment is initiated with a 6-hour intravenous (IV) infusion followed by oral ganaxolone or matching placebo. Additional subjects may be included into these cohorts or additional cohorts may be added, but will not exceed 100 randomized subjects for the study.

The screening period for each cohort will be up to 2 weeks. Following the screening period, there will be a 4-day inpatient treatment phase at a hospital or clinical pharmacology unit for Cohorts 1-5 during which a 60-hour infusion of ganaxolone or placebo will be administered (with or without bolus dosing). The subjects will be discharged from the unit on the morning of Day 4. There will be 2 safety follow-up visits after inpatient discharge on post-treatment Weeks 1 and 4.

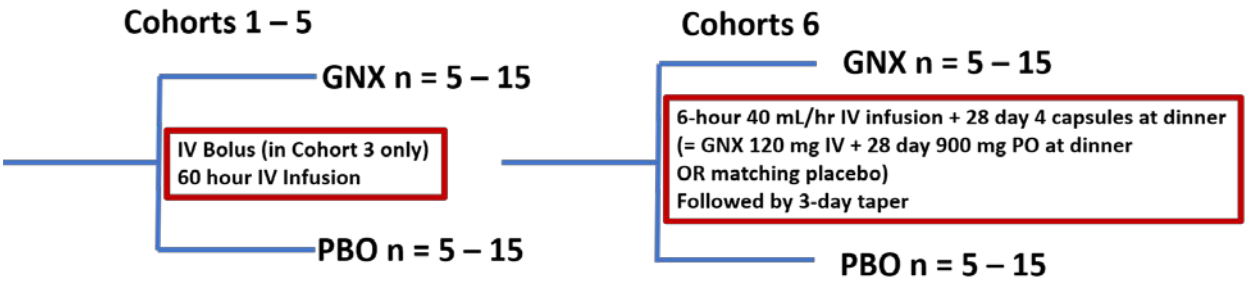
In Cohort 6, following the screening period, there will be a 1-day inpatient treatment phase at a hospital or clinical pharmacology unit during which a 6-hour infusion of ganaxolone or matching placebo will be administered initially from 9 am to 3 pm (±1 hour) before oral dosing is started at 7 pm (±1 hour). The subjects will be admitted on Day 0 and discharged from the unit in the morning of Day 2. The first dose of oral ganaxolone (4 capsules; 900 mg) or matching placebo will be administered at dinner time (around 7 pm) of Day 1, 4 hours after the end of infusion on Day 1. Oral dosing is continued as outpatient on Days 2-28. The dosing regimen during the outpatient phase of Cohort 6 is 900 mg or placebo (4 capsules) at dinner time daily. A 3-day taper will follow at days 29, 30, and 31, as described in Section 3.4.6. There will be 3 safety follow-up visits after the last dose on post-treatment Weeks 1,4, and 6.

On Day 1 subjects will have 6 PK samplings: at 1 hour after the end of the 6-hour infusion (i.e., at 4 pm), at 7 pm (just prior to the oral dosing), and at 1, 2, 3, and 4 hours post oral dosing (at 8, 9, 10, and 11 pm) as well at 8 am the following morning (on Day 2) prior to discharge.

The subjects will take a 900 mg dose or placebo (4 caps) on the evening of Day 1 at dinner time and continue with the 900 mg dose or matching placebo at dinner time on Days 2-28. A 3-day taper will follow as described in Section 3.4.6.

A schematic of the study design if provided in Figure 1.

Figure 1: Study Design Flow Chart



7.1 Screening Visit and Screening Period (day -14 to -1) – Cohorts 1-6

- Obtain written informed consent
- Collect demographics, medical history, review prior medications, review of concomitant medications and therapies,
- Assess CGI-S
- Conduct MINI international neuropsychiatric interview
- Conduct Hamilton Depression Rating Scale 17-item version (HAMD17) interview
- Edinburgh Postnatal Depression Scale (EPDS)
- Spielberger State-Trait Anxiety Inventory (STAI6)
- Perform a physical examination
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate)
- Collect ECG
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Collect safety laboratory tests
- Measure height and weight
- Conduct CSSRS interview
- Review inclusion and exclusion criteria. Screen failure is defined as a subject who has given informed consent, and failed to meet the inclusion criteria and/or met the exclusion criteria
- Schedule a SAFER interview if the subject meets the eligibility criteria. The SAFER interview will be conducted during the screening period. The investigative site must wait for the results of the SAFER interview before admitting the subject on the unit.

- Screening period may be extended to 21 days with approval from the medical monitor (e.g. a laboratory sample was hemolysed which had to be repeated causing a delay).
- The subject may stay on the inpatient unit voluntarily between screening visit and admission to the study (Day 0) provided that close monitoring of the subject can be ensured. The gap between the screening visit and admission (Day 0) should be kept as short as possible, preferably no more than 2 days. Q15 minute health checks should be implemented during the gap period. The SAFER interview will be done during the gap period. The sponsor should be informed of this decision.

7.2 Admission to the Unit (Day 0) – Cohorts 1-6

- Review concomitant medications and therapies
- Admission to the unit. The subject arrives on the unit the day before the start of the infusion (Day 1) to complete assessments and accommodate to the unit.
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate)
- Collect ECG
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Collect safety laboratory tests
- Collect neurosteroid level
- Measure weight
- CTNI to conduct HAMD17 interview
- Collect AEs
- Conduct CSSRS interview
- Review inclusion and exclusion criteria (including hematology and chemistry from the screening visit); HAMD17 (conducted by CTNI) must be ≥ 22 for randomization.
- Start Q15 minutes health checks (e.g. to observe general wellbeing and behavior, monitor infusion)
- If the subject is breastfeeding, she is encouraged to "pump and dump" while inpatient and for 45 days after the discharged from the unit. She should be provided with a breast pump.

7.3 Infusion Days (+ 1 to + 4) – Cohorts 1-5

7.3.1 Before Infusion (Morning of Day + 1)

- Review concomitant medications
- CTNI to conduct HAMD17 interview
- EPDS

- STAI6
- Assess CGI-S
- Collect AEs
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate)
- Stanford Sleepiness Scale (SSS)
- Conduct CSSRS interview
- Randomization
- Start monitoring of pulse oximetry
- The subject's bed should be placed close to the nursing station in an area that allows visual observation of the subject throughout the infusion period.

7.3.2 During Infusion (Days +1 to +4)

- Start bolus/infusion in the morning of Day +1 (0h) after baseline assessments are completed
- CTNI to conduct interviews for HAMD17 (+12h, +24h, +48h, +60h, +72h)
- Conduct interviews for CGI-I (+12h, +24h, +48h, +60h, +72h)
- EPDS (+60h)
- STAI6 (+12h, +24h, +48h, +60h, +72h)
- Collect AEs
- Collect ECG (+12h, +24h, +48h, +72h)
- Collect VS (BP, pulse, respiratory rate, pulse oximetry, temperature): (+4, +8h, +12, +18h, +24h, +32h, +40h, +48h, +56h, +60h, +72h)
- Collect SSS (+8h, +32h, +56h, +72h)
- Collect pharmacokinetic samples (+12h, +24h, +48h, +72h)
- Record concomitant medications
- Lower the infusion rate to half what was prescribed for the cohort (for example, lower the infusion rate from 4 mg/h to 2 mg/h) (+48h)
- Collect safety laboratory tests (+48h)
- Collect neurosteroid level (+48h)
- End infusion (+60h)
- Collect urine sample for urinalysis, drug screen and urine pregnancy test (+72h)
- Conduct CSSRS interview (+12h, +36h, +60h, +72h)
- Perform a physical examination (+72h)

- Stop monitoring of pulse oximetry and Q15 min health checks (+72h)
- Discharge subject (+72h)

7.4 Post Discharge Follow-up Period (Days +5 to +30) – Cohorts 1-5

7.4.1 First Post-discharge Visit 7 Days After Discharge from the Unit (Day +11; visit window)

- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate)
- Collect safety laboratory tests.
- Collect neurosteroid level
- Collect pharmacokinetic sample
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Measure weight
- Conduct interviews for HAMD17 (CTNI) and CGI-I
- EPDS
- STAI6
- Conduct CSSRS interview
- Collect AEs

7.4.2 Second Post-discharge Visit 30 Days After Discharge From the Unit (Day +34)

- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate)
- Measure weight
- Collect urine sample for urinalysis, drug screen and urine pregnancy test,
- Collect pharmacokinetic sample
- Conduct CSSRS interview
- Collect AEs
- Conduct interviews for HAMD17 (CTNI) and CGI-I
- EPDS
- STAI6

Table 1. Schedule of Assessments – Cohorts 1-5

Day	Day -14 to -1	Day 0	Day 1 (Start Infusion in AM, 0h)	Day 2	Day 3 (End Infusion in PM)	Day 4 (Discharge)	Day 11 (Day 7 Post Discharge)	Day 34 (Post Discharge Day 30)
VISIT	**Screening**	**Admission**	**Infusion**	**Infusion**	**Infusion**	**Discharge**	**Follow-up**	**Follow-up**
			0h-24	24-48h	48-72	72h		
Informed consent	X							
Demographics, Medical History	X							
MINI neuropsychiatric interview	X							
Inclusion/Exclusion criteria	X	X						
Concomitant Meds and Therapy Review	X	X	X	X	X	X	X	X
Admission to the unit		X						
Discharge from the unit						X		
Physical examination	X					X		
SAFER Interview (during screening)	X							
Vital signs (BP, Pulse, pO2, RR, temp)	X	X	X	X	X	X	X	X
Height (screening only) and weight	X	X					X	X
ECGs	X	X	X	X	X	X		
Safety Laboratory Tests	X	X			X		X	
Neurosteroid level		X			X		X	
Urinalysis, Drug Screen and Pregnancy Tests	X	X				X	X	X
CSSRS	X	X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X
Randomization			X					
Start bolus/infusion (0h)			X					
Lower the infusion rate to half (+48h)					X			
End infusion (+60h)					X			
PK sample collection			X	X	X	X	X	X
HAMD17	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X
CGI-S	X		X					
EPDS	X		X		X		X	X
SSS			X	X	X	X		
STAI6	X		X	X	X	X	X	X
Q15 min health checks & pulse ox			throughout					

Specific timepoints for assessments on days +1, +2, +3 and +4: - Cohorts 1-5

PK samples: +12h, +24h, +48h, +72h
HAMD17: before start of infusion, +12h, +24h, +48h, +60h, +72h all done by CTNI
CGI-I: +12h, +24h, +48h, +60h, +72h
CGI-S: before start of infusion
EPDS: before start of infusion, +60h
STAI6: before start of infusion, +12h, +24h, +48h, +60h, +72h
ECG: +12h, +24h, +48h, +72h
Vital Signs: (BP/P/pO2/RR/Temp): before start of infusion, +4, +8h, +12, +18h, +24h, +32h, +40h, +48h, +56h, +60h, +72h
SSS: before start of infusion, +8h, +32h, +56h, +72h
CSSRS: before start of infusion, +12h, +36h, +60, +72h
Safety laboratory tests and neurosteroid level: +48h
Urinalysis drug and pregnancy test: +72h
Physical examination: +72h
AEs and concomitant medications are collected throughout the inpatient stay.

Q15min health checks are done from the time of admission to the time of discharge. Pulse oximetry (pO2) must be monitored throughout the infusion, including during the night when the subject is sleeping. The subject should be awakened if pulse oximetry falls < 91%.

The following priority order will be in effect when more than 1 assessment is required at a particular time point: 1) HAMD17 2) CGI-I/CGI-S 3) EPDS 4) STAI6 5) SSS 6) CSSRS 7) vital signs 8) ECG 9) safety labs and neurosteroid level 10) PK sample 11) neurosteroid level 12) urinalysis drug screen and pregnancy test 13) physical examination

Day 11 and Day 34 visits have visit windows of ± 3 and ± 5 days, respectively

7.5 Infusion (Day +1) – Cohort 6 (Screening and Admission visits for Cohort 6 described in Section 7.1 and 7.2, respectively)

7.5.1 Before Infusion (Morning of Day +1; Baseline)

- CTNI to conduct HAMD17 interview
- EPDS
- STAI6
- Assess CGI-S
- Review concomitant medications
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate),
- Stanford Sleepiness Scale (SSS)
- Conduct CSSRS interview
- Collect AEs
- Randomization
- The subject's bed should be placed close to the nursing station in an area that allows visual observation of the subject
- Start monitoring of pulse oximetry

7.5.2 During the Infusion and Evening of Day +1 (Day +1)

- Start 6-hour infusion at 40 mL/hr at 9 am of Day +1 (0h) after baseline assessments are completed (listed above)
- End 6-hour infusion
- Complete +6h assessments after the end of the 6-hour infusion CTNI to conduct interviews for HAMD17 (+6h)
- Conduct interviews for CGI-I (+6h)
- EPDS (+6h)
- STAI6 (+6h)
- Collect AEs
- Collect ECG (+6h)
- Collect VS (BP, pulse, respiratory rate, pulse oximetry, temperature): (+6h)
- Collect SSS (+6h)
- Collect pharmacokinetic samples (+7h [i.e., 1 hour after the end of the infusion], at +10h [i.e., just before the oral dose], and at 1, 2, 3, and 4 hours after the oral dose
- Collect neurosteroid level (+6h)
- Record concomitant medications
- Conduct CSSRS interview (+6h)

- Administer the IP: 900 mg of ganaxolone, or matching placebo (four 225 mg capsules or four placebo capsules), at dinner time (i.e., at 7 pm) ±15 minutes of a fatty meal or snack (e.g., fatty yogurt, nuts, avocado)
- Continue monitoring of pulse oximetry and Q15 min health checks

7.5.3 Day + 2 (Discharge and transition to outpatient treatment)

- The assessments listed below are completed before discharge
- CTNI to conduct interviews for HAMD17
- Conduct interviews for CGI-I
- EPDS
- STAI6
- Collect AEs
- Collect ECG
- Collect VS (BP, pulse, respiratory rate, pulse oximetry, temperature)
- Collect SSS
- Collect a pharmacokinetic sample at 8 am (23h)
- Collect neurosteroid level
- Record concomitant medications
- Conduct CSSRS interview
- Perform physical examination
- Dispense medication bottle
- Provide the subject with dosing instructions and subject diary completion.
- Subject will take the IP (900 mg dose of ganaxolone, or matching placebo) at dinner time (four 225 mg capsules, or matching placebo capsules)

7.6 Outpatient treatment phase (Days + 3 – +29) - Cohort 6

7.6.1 Safety phone calls (Days +3, +5, +10 and +13)

- A safety phone call is made on days +3, +5, +10, and +13 by the PI (or the sub-I). The subject is asked about her general wellbeing. AEs are recorded.

7.6.2 Visit 3 HAMD Call (Day +4 ±1 day)

- CTNI to conduct HAMD17 interview

7.6.3 Visit 4 (Day +8)

- CTNI to conduct HAMD17 interview
- EPDS
- STAI6
- Assess CGI-I
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate),
- Collect ECG
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Collect safety laboratory tests
- Collect neurosteroid level
- Collect a pharmacokinetic sample
- Stanford Sleepiness Scale (SSS)
- Conduct CSSRS interview
- Collect AEs
- Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions. IP return and accountability.
- Subject will continue to take study drug (900 mg of ganaxolone, or matching placebo) at dinner time (unless the dose is lowered to 675 mg, or 450 mg, or matching placebo at dinner time as per instructions from the investigator)

7.6.4 Visit 5 HAMD Call (Day +11 ±1 day)

- CTNI to conduct HAMD17 interview

7.6.5 Visit 6 (Day +15 ±2 days)

- CTNI to conduct HAMD17 interview
- EPDS
- STAI6
- Assess CGI-I
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate),
- Collect ECG

- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Collect safety laboratory tests
- Collect neurosteroid level
- Collect a pharmacokinetic sample
- Measure weight
- Stanford Sleepiness Scale (SSS)
- Conduct CSSRS interview
- Collect AEs
- Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions. IP return and accountability.
- Perform physical examination

7.6.6 Visit 7 (Day +22 ±3 days)

- CTNI to conduct HAMD17 interview
- EPDS
- STAI6
- Assess CGI-I
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate),
- Collect ECG
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Collect neurosteroid level
- Collect a pharmacokinetic sample
- Stanford Sleepiness Scale (SSS)
- Conduct CSSRS interview
- Collect AEs
- Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions. IP return and accountability.

7.6.7 Visit 8 (Day +29 ±3 days)

- CTNI to conduct HAMD17 interview

- EPDS
- STAI6
- Assess CGI-I
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate),
- Collect ECG
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Collect safety laboratory tests
- Collect a pharmacokinetic sample
- Measure weight
- Stanford Sleepiness Scale (SSS)
- Conduct CSSRS interview
- Collect AEs
- Dispense study medication with a supply to last through the taper period. Provide the subject with dosing instructions. IP return and accountability.
- Begin 3-day taper (3 capsules on Day 29, 2 capsules on Day30, 1 capsule on Day31, or, if Day 28 dose is other than ganaxolone 900 mg or placebo, follow instructions in section 3.4.6)
- Perform physical examination

7.7 Post–treatment Follow-up Period (Days +29 to +71) – Cohort 6

7.7.1 First Post-treatment Follow-up Visit - 7 days After the Last On-treatment Visit (Day +36)

- The Follow-up Visit 1 should occur about 1 week after the Day 29 visit.
- CTNI to conduct interviews for HAMD17
- Perform EPDS
- Perform STAI6
- Assess CGI-I
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- Collect ECG Collect neurosteroid level
- Collect a pharmacokinetic sample
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Measure weight

- Conduct CSSRS interview
- Collect SSS
- Collect AEs
- IP return and accountability

7.7.2 Second Post-treatment Follow-up Visit - 28 days After the Last On-treatment Visit (Day +57)

- The Follow-up Visit 2 should occur about 28 days after the Day 29 visit.
- CTNI to conduct interviews for HAMD17
- Perform EPDS
- Perform STAI6
- Assess CGI-I
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- Collect safety laboratory tests
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Measure weight
- Conduct CSSRS interview
- Collect SSS
- Collect AEs

7.7.3 Third Post-treatment Follow-up Visit - 42 days After the Last On-treatment Visit (Day +71)

- The Follow-up Visit 3 should occur about 42 days after the Day 29 visit.
- CTNI to conduct interviews for HAMD17
- Perform EPDS
- Perform STAI6
- Assess CGI-I
- Review concomitant medications and therapies
- Collect vital signs (BP, pulse, temperature, RR)
- Collect urine sample for urinalysis, drug screen and urine pregnancy test
- Measure weight
- Conduct CSSRS interview
- Collect SSS
- Collect AEs

Table 2. Schedule of Assessments – Cohort 6

Day	Day -14 to -1	Day 0 Admission	Day 1	Day 1[e]	Day 2[f]	Days 3 & 5	Day 4	Day 8	Days 10 & 13	Day 11	Day 15	Day 22	Day 29	Day 36	Day 57	Day 71
VISIT	Screening		Baseline	Post-BL	Discharge & Outpatient	Safety call	V3 HAMD Call	V4 outpt	Safety call	V5 HAMD Call	V6 outpt	V7 outpt	V8 outpt	1st Follow-up	2nd Follow-up	3rd Follow-up
Informed consent	X															
Demographics, Medical History	X															
MINI neuropsychiatric interview	X															
Inclusion/Exclusion criteria	X	X														
Concomitant Meds and Therapy Review	X	X	X	X	X			X			X	X	X	X	X	X
Admission to the unit		X														
Discharge from the unit					X											
Physical examination	X				X						X		X			
SAFER Interview (during screening)	X															
Vital signs (BP, Pulse, pO2, RR, temp)	X	X	X	X	X			X			X	X	X	X	X	X
Height (screening only) and weight	X	X									X		X	X	X	X
ECGs	X	X		X	X			X			X	X	X	X		
Safety Laboratory Tests	X	X						X			X		X		X	
Neurosteroid level		X		X	X			X			X	X		X		
Urinalysis, Drug Screen and Pregnancy Tests	X	X						X			X	X	X	X	X	X
CSSRS	X	X	X	X	X			X			X	X	X	X	X	X
Record AEs		X	X	X	X	X		X	X		X	X	X	X	X	X
Randomization			X													
Start infusion (0h; 9 am ±1h)[a]				X												
End infusion (6h)				X												
PK sample collection[b]				X	X			X			X	X	X	X		
HAMD17[c]	X	X	X	X	X		X	X		X	X	X	X	X	X	X
CGI-I				X	X			X			X	X	X	X	X	X
CGI-S	X		X													
EPDS	X		X	X	X			X			X	X	X	X	X	X
SSS			X	X	X			X			X	X	X	X	X	X
STAI6	X		X	X	X			X			X	X	X	X	X	X
Dispense medication/return accountability					X			X			X	X	X			
Oral dosing (at dinner time)				X	throughout the outpatient period											
Q15 min health checks & pulse ox[d]		X	throughout the inpatient period													
Start 3-day taper													X			

[a] Infusion starts at 9 am and ends 6 hours later at 3 pm and is administered at a constant rate of 40 mL/hr.

[b] Twelve pharmacokinetic samples are collected in Cohort 6:

On Day 1 subjects will have 6 PK samplings: at 1 hour after the end of the 6-hour infusion (i.e., at 4 pm), at 7 pm (just prior to the oral dosing), and at 1, 2, 3, and 4 hours post oral dosing (at 8, 9, 10, and 11 pm) as well at 8 am the following morning (on Day 2) prior to discharge.

A pharmacokinetic sample is also collected on Days 8, 15, 22, 29, and 36 during the study visit.

[c] All HAMD17 ratings, except the one done at screening, will be conducted by CTNI raters.

[d] Q15min health checks are done from the time of start of the infusion to the time of discharge. Pulse oximetry (pO2) must be monitored from the start of the infusion throughout the inpatient period, including during the night when the subject is sleeping. The subject should be awakened if pulse oximetry falls < 91%.

[e] On Day +1 all efficacy assessments should be conducted first before lab draws, if possible.

[f] All Day +2 assessments, including PK and neurosteroid levels, are to be done before the subject is discharged from the unit.

The following priority order will be in effect when more than 1 assessment is required at a particular time point: 1) HAMD17 2) CGI-I/CGI-S 3) EPDS 4) STAI6 5) SSS 6) CSSRS 7) vital signs 8) ECG 9) safety labs and neurosteroid level 10) PK sample 11) neurosteroid level 12) urinalysis drug screen and pregnancy test 13) physical examination

All outpatient visits have a ± 3-day visit window, except Visits 3 and 5 which have just a ± 1-day visit window and Visits 4 and 6 which have a ± 2-day visit window.

7.8 Study Evaluations and Procedures

7.8.1 Demographic, Medical History and Other Baseline Characteristics

Demographic and Other Baseline Characteristics will be collected and recorded on the appropriate sections of the eCRF at the time of the screening visit.

7.8.2 Informed Consent

The nature of the study and its risks and benefits will be explained to the subject by the principal investigator or designated study personnel. The purpose of placebo control design and the chances of receiving placebo in this study will be discussed with the subject.

7.8.3 Eligibility Review

An eligibility review will be conducted by the investigator at the visits specified in Table 1 or 2 using the subject inclusion and exclusion criteria below.

7.8.4 Prior Medication, Concomitant Medication and Concomitant Therapy Review

At screening, prospective subjects will be asked about medications they have taken in the previous 60 days, including prescription medications, non-prescription medications, vitamins and supplements. At subsequent visits, the subjects will be asked about medications taken since the last visit. During the inpatient treatment phase concomitant medications taken by the subject will be recorded.

The medications that were taken within the past 60 days will be recorded. The medications that were taken within the past 60 days but stopped before the screening visit are recorded on the prior medications eCRF page. The medications that were taken during the study period between the screening visit and last follow-up visit, regardless of whether the medication was started during the study period or before the study period, are recorded on the concomitant medications eCRF page.

The following data will be recorded for all medications used by the subject: drug name, dose, regimen, route of administration, start and stop dates, and the indication for use.

The type of psychological counseling the patient is receiving at the time of screening will be recorded on the Concomitant Psychological Treatment eCRF page.

7.8.5 Physical Examination

A complete physical examination will be performed at screening, before discharge from the unit, and during visits 6 and 8 (outpatient visits) of Cohort 6.

The physical examination will include a review of the following body systems:

- General appearance

- Skin
- Head, Eyes, Ears, Nose, Mouth and Throat
- Neck/Thyroid/Breastfeeding status
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen

The physical examination will be documented in the subject's source documents and on the physical examination eCRF. If a new clinically significant abnormal finding (i.e. not noted at screening) occurs after the screening examination, it must be captured as an AE and documented on the appropriate AE eCRF page.

7.8.5.1 12-lead Electrocardiogram

A 12-lead ECG will be conducted at the time points described in Table 1 or 2. Before each measurement the subject should be resting in a supine or semi-recumbent position for 10 minutes. RR, PR, QRS, QTcF and QTcB will be collected. ECGs will be measured with equipment calibrated as per the ECG vendor's standard operating procedure. The ECG results will be assessed by a qualified clinician. The Investigator's assessment of Normal or Abnormal will be recorded and entered in the eCRF page. If a new clinically significant abnormal finding (i.e. not noted at Screening) occurs after the Screening examination, it must be captured as an AE or SAE (if it meets criteria for an SAE – see Section 8.0) and documented on the appropriate AE eCRF page and, if an SAE, submitted to Marinus Safety Department on the SAE form.

7.8.5.2 Clinical Safety Laboratory Evaluations

The name and address of the central clinical laboratory for this study will be maintained in the Investigator's files at each study site.

All clinical laboratory assays will be performed according to the laboratory's normal procedures as described in Table 1 or 2.

Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the values are clinically significant or not. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The following clinical laboratory assessments will be performed:

Biochemistry

Sodium, potassium, glucose, chloride, carbon dioxide, creatinine, total protein, blood urea nitrogen, albumin, total bilirubin (with reflex fractionation to direct and indirect bilirubin if total bilirubin is elevated and outside of the normal range), alanine aminotransferase, aspartate transferase, alkaline phosphatase, thyroid stimulating hormone (with reflex to free T4 if thyroid stimulating hormone (TSH) is outside of the normal range). The PI may determine serum βHCG levels to confirm or exclude pregnancy.

Hematology

Hematocrit, hemoglobin, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, white blood cell count with differential.

Subjects are not required to be fasting prior to collection of the blood samples.

Urine analysis including pregnancy test and urine drug screen

Leukocytes, nitrites, protein, blood, specific gravity, glucose, ketones, urine pregnancy test, urine drug screen (cannabis, opioids [including oxycodone, methadone and buprenorphine], cocaine, benzodiazepines, barbiturates, alcohol [ethanol], and phencyclidine).

Confirmatory testing of positive drug screen findings using for example gas chromatography mass spectroscopy (GCMS) may be conducted.

7.8.5.3 Adverse Event Collection

Please refer to Section 8.0, Adverse and Serious Adverse Events Assessment.

7.8.5.4 Vital Signs

Vital signs including blood pressure, pulse, respirations, temperature (recorded in Celsius [°C]) and pulse oximetry will be monitored at the time points as outlined above. Vital signs should be collected after the subject has been supine for 5 minutes. If a vital sign measurement is scheduled at the same time as a blood draw, vital signs should be collected prior to the blood draw. Blood pressure should be determined by an appropriately-sized cuff (using the same method, the same arm and in the same position throughout the study). Any abnormal screening vital sign results considered to be clinically significant should be repeated to confirm the finding. Height (in centimeters) will be collected at the screening visit. Weight (in kilograms) will be collected at the screening and 2 follow-up visits.

During the inpatient phase while the subject is receiving study drug subjects should be monitored for pulse oximetry continually, including during the nights. Monitoring may be interrupted for bathroom breaks, lunch etc.

If pulse oximetry drops below 91% the patient should be wakened and assessed for excessive sedation.

Any clinically significant deviations from baseline vital signs that are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.8.6 **Interviews, Questionnaires and Scales**

The scales and assessments are listed in Appendix 2. A separate file containing each scale/assessment will be provided to the site.

7.8.6.1 Mini International Neuropsychiatric Interview 7.0

The Mini International Neuropsychiatric Interview (MINI) is a short, clinician-administered, structured diagnostic interview, with an administration time of approximately 15 minutes. The MINI will be administered at the screening visit.

7.8.6.2 The Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAMD) is a commonly-used semi-structured clinician-rated instrument which assess the range of symptoms that are most frequently observed in subjects with major depression. HAMD has undergone a considerable amount of psychometric study and is accepted as a valid standard of symptom outcome assessment in studies of major depression. In this study the symptoms of depression will be scored using the original 17-item HAMD scale (HAMD17). The 6-item version of this scale, known as HAMD6, will be derived from these data and used as an additional measure of changes in symptoms of depression. The items on the HAMD6 scale are as follows: depressed mood, work and interests, general somatic symptoms (tiredness), anxiety, guilt feelings, and psychomotor retardation. Both HAMD6 and HAMD17 have been validated and used in many clinical trials of antidepressant medications.[9] The use of the 6-item scale is justified because many items on the 17-item version cannot be expected to change over short period of time (e.g. weight or sleep). All HAMD17 ratings, except the one done at screening, will be conducted by CTNI raters.

7.8.6.3 Stanford Sleepiness Scale

Stanford Sleepiness Scale (SSS) is a simple 8-item self-rated scale measuring level of sleepiness the subject is feeling. Level 1 is “feeling active, vital, alert or wide-awake” level 7 is “no longer fighting sleep, sleep onset soon; having dream-like thoughts”; level 8 is sleeping.

7.8.6.4 Clinical Global Impression-Improvement (CGI-I) and Clinical Global Impression-Severity (CGI-S)

The Clinical Global Impression – Improvement scale (CGI-I) is a 7-point scale that asks the clinician to assess how much the subject's illness has improved or worsened relative to a baseline state at the beginning of the intervention. It is rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. The Clinical Global Impression – Severity scale (CGI-S) is a 7-point scale

that asks the clinician to rate the severity of the subject's depression at the time of assessment, relative to the clinician's past experience with subjects who have the same diagnosis. Considering total clinical experience, a subject is assessed on severity of depression at the time of rating 1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

7.8.6.5 Edinburgh Postnatal Depression Scale (EPDS)

The (EPDS) is a 10-question self-rated instrument for assessment symptoms of PPD, such as worry, sleep, mood and enjoyment. Two questions assessing obsessive thoughts are added to this questionnaire ("How much of your time is occupied by obsessive thoughts over the past 24h?" and "How much distress do your obsessive thoughts cause you?), but they are not counted towards the total score in the statistical analysis. These 2 questions are rated on a 5-point scale.

7.8.6.6 Spielberg Trait-State Anxiety Inventory, 6 item version

The Spielberg Trait-State Anxiety Inventory, six item version (STAI6) is a short questionnaire evaluating anxiety state. The STAI6 has 6 questions, such as "I feel calm" and "I feel tense," which the subject rates on a scale corresponding to "not at all," "somewhat," "moderately," and "very much."[12]

7.8.6.7 SAFER interview

Staff psychiatrists or psychologists at the Massachusetts General Hospital Clinical Trials Network and Institute (CTNI) will perform independent remote SAFER interview (State versus trait; Assessability; Face validity; Ecological Validity; and Rule of 3 Ps (pervasive, persistent, and pathological)) for the screened subjects who are deemed eligible for randomization to confirm validity of the diagnosis of PPD and eligibility for the study from depression perspective.

7.8.7 **Columbia Suicide Severity Rating Scale (CSSRS)**

The CSSRS is a unique, simple, and short method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality.[13] It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents) that are significantly predictive of completed suicide.

7.8.8 **Pharmacokinetic Sampling**

Blood samples for pharmacokinetic analysis will be drawn at the times specified in Tables 1 and 2 to allow determination of ganaxolone plasma levels.

7.8.9 **Neurosteroid levels**

A sample for determination of neurosteroid levels (allopregnanolone and possibly other progesterone metabolites) will be drawn at the times specified in Tables 1 and 2.

7.8.10 Volume of Blood to Be Drawn from Each Subject

Table 3. Volume of Blood to Be Drawn from Each Subject (Cohorts 1-5)

Assessment	Approximate Sample Volume (mL)[a]	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples	6	6	36
Safety hematology	3	4	12
Safety chemistry	7	4	28
Neurosteroid level	6	3	18
Total mL			94

During this study, approximately 94 mL of blood will be drawn from all subjects during the study (Cohorts 1-5).

Table 4. Volume of Blood to Be Drawn from Each Subject (Cohort 6)

Assessment	Approximate Sample Volume (mL)[a]	Number of Samples	Approximate Total Volume (mL)
Pharmacokinetic samples	6	12	72
Safety hematology	3	6	18
Safety chemistry	7	6	42
Neurosteroid level	6	7	42
Total mL			174

Approximately 174 mL of blood will be drawn from all subjects during the study (Cohort 6).

8.0 ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (e.g. "Have you had any health problems since the previous visit/you were last asked?"). All AEs are collected from the time the informed consent is signed until the end of the follow-up period. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure, regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached (AE has resolved), stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. Any changes in the severity of the AE must be recorded.

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Causality Categorization

The investigator will assess causal relationship between the investigational product and each AE (i.e., their relationship to study drug), and answer "yes" or "no" to the question, "*Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?*"

8.1.3 Variables

The following variables will be collected for each AE:

- AE
- The date and time when the AE started and stopped
- Maximum intensity or intensity or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against the study drug (yes or no)
- Action taken with regard to investigational product (none, dose reduced, interrupted, withdrawn)
- AE caused subject's discontinuation from study *(*yes or no*)*
- Outcome (fatal, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, recovered/resolved, unknown)

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study (e.g. depression) should not be classified as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Adverse Events Based on Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory, vital sign, or ECG assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a there is a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g. concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign, or ECG parameter is clinically significant and therefore represents an AE.

8.1.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "*Have you had any health problems since the previous visit/you were last asked?"* or revealed by observation, will be collected and recorded in the eCRF.

8.1.7 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the end of the follow-up period.

Any report of pregnancy for any study participant must be reported within 24 hours to Marinus Safety Department or its delegate using the Pregnancy Report Form (and any applicable follow-up reports). The study participant must be withdrawn.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Marinus Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Marinus Serious Adverse Event Form to Marinus Safety Department. The test date of the first positive serum/urine β-human chorionic gonadotropin (β-HCG) test or ultrasound result will determine the pregnancy onset date.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the Investigator's Brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to Marinus Safety Department within 24 hours of the first awareness of the event.

The investigator must complete, sign, and date the Marinus Serious Adverse Event Forms and verify the accuracy of the information recorded on the form with the corresponding source documents and fax or e-mail the form to:

Email: safetyPPD2002@marinuspharma.com

Fax: 484-679-2138

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless they result in an SAE.

8.2.3 Serious Adverse Event Definition

A serious adverse event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- **Results in death**
- **Is life-threatening.** Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization.** Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as an SAE(s).
- **Results in persistent or significant disability/incapacity**
- **Is a congenital abnormality or birth defect**
- **Is an important medical event.**

  Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the end of the follow-up period and must be reported to the Marinus Safety Department or its delegate within 24 hours of the first awareness of the event. In addition, the Marinus medical monitor should be informed of the event within 24 hours via either email or a phone call.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Marinus Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the date the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (i.e. the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g. drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received the investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor or its delegate is responsible for notifying the relevant regulatory authorities of related, unexpected SAEs.

In addition, the sponsor or its delegate is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the ganaxolone clinical development program.

The investigator is responsible for notifying the local Institutional Review Board (IRB), local Ethics Committee (EC), or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9.0 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRFs. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is enrolled, it is expected that site personnel will complete the eCRF entry within approximately 2 business days of the subject's visit. During the inpatient phase the site must complete the eCRF entry daily (every evening) to allow monitoring of the data.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the eCRF completion guidelines or data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Data that may potentially unblind the treatment assignment (i.e. investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4 Handling of Missing and Incomplete Data

While every attempt must be made by the Investigator to provide complete data, there are cases in which this may not always be possible (e.g. incomplete subject recall of start and stop dates). Unrecorded values will be treated as missing, except for severity and relationship to investigational medicinal product for AEs. If the severity or relationship to investigational medicinal product is missing for an AE, which occurred post administration of investigational medicinal product, the event will be regarded as severe and related to investigational medicinal product, respectively.

The appropriateness of the method(s) described for handling missing data for other variables will be reassessed at data reviews. Any necessary changes or refinements will be documented in the Statistical Analysis Plan (SAP). Depending on the extent of missing values, further investigation may be made into the sensitivity of the analysis results, to the method(s) specified.

9.5 Statistical Analysis Plan

Data analyses will primarily be descriptive. The purpose of this study is to identify a ganaxolone dose and exposure level that is safe and well tolerated. Efficacy data will be collected but will be considered hypothesis-generating i.e., there are no *a priori* hypotheses on which the study was powered. Results from exploratory statistical analyses may be presented but only to aid in interpretation.

The SAP will provide the statistical methods and definitions for the analysis of the safety and efficacy data, and it will describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, or unused data will be addressed.

The SAP will be finalized prior to completion of the first cohort to preserve the integrity of the statistical analysis and study conclusions. This will not preclude amendments to the SAP before database lock.

9.5.1 Planned Interim Analysis

Safety and efficacy data from each cohort will be unblinded, and analyses will be conducted for the purpose of dose selection for the next cohort. The dose for the next cohort will be decided based on these interim data analyses. The decision how to adjust the dose and/or the duration of the infusion will be made based on recommendations by a Data Review Committee (DRC) composed of the sponsor's Chief Medical Officer, and at least 2 other external physicians. At least one of the members will have special expertise in the clinical care of women with depression or postpartum depression. One of the members will have expertise in the conduct of clinical trials or analysis of clinical trial data. The study team and all parties other than the DRC will remain blinded.

The dose for the subsequent cohorts will be selected with the goal of gaining additional information on ganaxolone's tolerability and dose-response profile.

A separate DRC guidance document outlines the principles for dose selection. Marinus may decide to stop the study, or make the data public, after completion of any cohort.

9.5.2 Justification for Sample Size

No formal hypothesis testing will be performed and the sample size is not based on statistical power considerations. The sample size was chosen based on experience with other studies conducted with compounds in early clinical development. A population of about 6 to 10 subjects per dose is commonly tested in studies which aim to establish a tolerability range for a new compound or a new formulation, and is used as a guide for a minimum cohort size for this study.

Similar study design was recently used to assess safety and identify an efficacy signal in major depressive disorder for NSI-189.[3]

9.5.3 Study Population

The **Screened Set** will consist of all subjects who have signed an informed consent.

The **Randomized Set** will consist of all subjects randomized.

The **Safety Set** will consist of all subjects who received IP.

The **modified Intent to Treat Set** (mITT) will consist of all subjects in the Safety Set who have at least 1 post-randomization efficacy assessment.

The **Per-Protocol Set** will consist of all subjects in the mITT set who do not have major protocol deviations that may affect key efficacy endpoints.

The **Infusion Completer Set** will consist of all subjects in the Safety Set who completed the 60-hour infusion in Cohort 1-5, and who completed the initial infusion in Cohort 6.

The **Completer Set** will consist of all subjects in the Safety Set who completed the 60-hour infusion and attended the final safety follow-up visit in Cohorts 1-5. In Cohort 6 the completer set will consist of subjects who completed the initial infusion and oral IP dosing period with at least 80% oral dosing compliance and attended all outpatient visits including the safety follow-up visits.

9.5.4 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics as well as subject disposition will be presented by treatment group.

Baseline characteristics will include a summary of the following:

- Subject demographics
- Pre-existing medical conditions
- Prior therapies.

Continuous variables such as age, weight, and height will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables, like sex and race, will be summarized using number of observations and percentages.

Medical history will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.

9.5.5 Investigational Medicinal Product

Summary statistics for the duration of exposure to investigational medicinal product will be presented by treatment group.

9.5.6 **Concomitant Medication**

Concomitant medications will be listed and summarized by preferred drug name and treatment group.

9.5.7 **Safety Analyses**

Reported AE terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of Treatment Emergent AEs (TEAEs), defined as any AE that started or worsened after first administration of IP, will be summarized by treatment group, system organ class preferred terms, severity and relatedness for each cohort. SAEs and AEs leading to discontinuation of the study drug will be listed separately for each cohort.

The absolute values and change from baseline in laboratory tests, vital signs, SSS, ECGs and CSSRS will be summarized by treatment group for each cohort.

Potentially clinically important findings will be included in AE summaries and listings.

Results of the physical examination (baseline and discharge) will be listed.

9.5.8 **Efficacy Analyses**

9.5.8.1 Primary Endpoint

The primary efficacy endpoint will be HAMD17 total score change from baseline to 60 hours post-infusion (on Day 3) for Cohorts 1-3 and to Day 29 for Cohort 6. The primary analysis in each cohort will be done using the mITT set. Although the trial is not powered for inferential analysis and there is no consideration for control of type 1 error across multiple cohorts, a clinically meaningful numeric difference in means of 3-4 points between ganaxalone and placebo treatment groups would be considered an indication of efficacy and will be the most influential outcome in the overall assessment of the efficacy of ganaxalone in treating PPD.

9.5.8.2 Secondary Endpoints

The trial will also evaluate the following secondary endpoints at each post-baseline data collection time point to provide additional evidence of the efficacy of ganaxalone in treating PPD:

- Change from baseline in HAMD17 total score other than at 60 hours post-infusion (on Day 3) for Cohorts 1-3 and to Day 29 for Cohort 6
- HAMD17 response defined as at least a 50% reduction from baseline in total score
- HAMD17 remission defined as total score <= 7
- Change from baseline in EPDS total score
- Change from baseline in STAI6
- CGI-I

9.5.8.3 Exploratory Endpoints

[redacted]

9.5.8.4 Statistical Methods

Observed values and changes from baseline for HAMD17, EPDS, and STAI6 total scores, subscales, and individual items will be summarized by visit. The categorical outcomes of HAMD17 response, HAMD17 remission, and CGI-I will be summarized by visit.

The preferred approach for exploratory analysis of continuous efficacy variables will be mixed model repeated measures (MMRM) but other approaches such as t-tests, analysis of covariance, or non-parametric methods may be used if necessary or more practical. Similarly, the preferred approach for analysis of categorical efficacy variables will be repeated measures (e.g., generalized estimating equations) but other approaches such as chi square or Fisher's exact tests may be used.

9.5.9 **Other Analyses**

No other analyses are planned in this study.

9.5.10 **Pharmacokinetic Analyses**

The following pharmacokinetics parameters will be estimated for each subject receiving ganaxolone, if sufficient data are available: Maximal plasma concentration (C_{max}), concentration at steady-state (C_{ss}, determined by the mean concentrations once steady-state is achieved by visual inspection), AUC_{0-24} (calculated as C_{ss} multiplied by 24 hours). PK samples will be collected from subjects participating in Cohort 6 after the IV infusion, before and during the oral dosing portion of the study.

10.0 SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH), European Union (EU) Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g. CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained personnel are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub-investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all

observations and other data pertinent to the clinical investigation. CRFs must be completed by the investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the eCRF. All data sent to the sponsor must be endorsed by the investigator.

The Clinical Research Associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, including past psychiatric history.

The investigator must permit authorized representatives of the sponsor; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor will check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g. subject's medical file, appointment books, original laboratory reports, X-rays etc.).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g. the US FDA) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare Products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for

ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

If local IRB/EC is used, the principal investigator provides the sponsor or its delegate with a copy of the consent that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented prior to study start that another party (i.e., CRO or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor or delegate.

10.3.2 Institutional Review Board or Ethics Committee

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor or its delegate has received written IRB/EC approval of and copies of revised documents.

The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All sites and laboratories or entities providing support for this study, must, where applicable, comply with the HIPAA act of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor or its delegate.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives may review their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor in verifying the accuracy of the data (e.g. to confirm that laboratory results have been assigned to the correct subject).

The results of studies - containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results and Publication Policy

Marinus will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, public presentations to the investors in the company, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific or company website, or other disclosure of the study results, in printed, electronic, oral or other form. The results may be made public after completion of any cohort.

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12.0 APPENDICES

Appendix 1. Prohibited Strong CYP3A4 Inhibitors and Inducers

Prohibited strong inhibitors	**Prohibited strong inducers**
Indinavir	Efavirenz
Nelfinavir	Nevirapine
Ritonavir	Barbiturates
Clarithromycin	Carbamazepine
Itroconazole	Enzalutamide
Ketoconazole	Glucocorticoids
Nefazadone	Modafinil
Saquinavir	Oxcarbazepine
Suboxone	Phenobarbital
Telithromycin	Phenytoin
Grapefruit juice	Pioglitazone
	Rifabutin
	Rifampin
	St. John's Wort
	Troglitazone

Source: The Flockhart Table (http://medicine.iupui.edu/clinpharm/ddis/main-table)

Appendix 2. Scales and Assessments

The following scales/assessments will be utilized in this study:

Full Title of Scale/Assessment	Version
Hamilton Depression Rating Scale (HAMD17)	17-item version
Spielberg Trait-State Anxiety Inventory	6-item version
Edinburgh Postnatal Depression Scale (EPDS)	Two obsession items are added to the standard EPDS questionnaire
Columbia Suicide Severity Rating Scale	Baseline and since last visit (standard)
Stanford Sleepiness Scale	NA
Mini International Neuropsychiatric Assessment	Version 7.0
Clinical Global Impression - Improvement	NA
Clinical Global Impression - Severity	NA

A separate master file containing each scale/assessment listed above will be provided to the site. Updates to scales/assessments during the study (if applicable) will be documented in the table above and a new master file containing the revised scale/assessment will be provided to the site.

Appendix 3. Protocol History and Summary of Changes

Document	Date	Global/Country/Site Specific
Original Protocol	05 Dec 2016	US
Amendment 1 (V 2.0)	15 February 2017	US
Amendment 2 (V 3.0)	10 October 2017	US
Amendment 3 (V 4.0)	19 October 2017	US
Amendment 4 (V 5.0)	01 February 2018	US
Amendment 5 (V 6.0)	28 February 2018	US
Amendment 6 (V 7.0)	09 May 2018	US
Amendment 7 (V 8.0)	08 Oct 2018	US

Amendment 7 (V 8.0) Summary of Changes:

Page	Section, Title, Paragraph, Line	Original Text	Revised Text
All	Header	Version 7.0 / 09 May 2018	Version 8.0 / **08 Oct 2018**
1	Cover Page	Blank	**AMENDMENT 7 (V 8.0)** **08 Oct 2018**
Reason for Change: Updated amendment / version details			
2	Protocol Signature Page	[redacted], MD, PhD, [redacted] Clinical Development	[redacted] **MD** [redacted] **Clinical Development and Pharmacovigilance**
Reason for Change: Marinus contact change			
3	[redacted]	[redacted] MD, PhD [redacted], Clinical Development Medical Monitor Telephone: [redacted] Email: [redacted]	[redacted] **MD** **Telephone:** [redacted] **Email:** [redacted]
Reason for Change: Marinus contact change			
11	Study Synopsis	**Number of subjects (total and for each treatment arm):** This is a Phase 2A, double-blind, placebo-controlled, multiple-dose escalation study consisting of up to 6 cohorts (Cohorts 1-6). Approximately 200 women with PPD 18 to 45 years of age will be screened to randomize up to 100 subjects across up to 6 cohorts. Approximately 10-30 subjects will be randomized into each cohort. Randomized subjects will receive ganaxolone or placebo in a 1:1 ratio. In Cohorts 1-5 the treatment will be administered intravenously over 60 hours. In Cohort 6 the treatment is initiated with an intravenous (IV) infusion followed by a transition to oral ganaxolone for 14 days.	**Number of subjects (total and for each treatment arm):** This is a Phase 2A, double-blind, placebo-controlled, multiple-dose escalation study consisting of up to 6 cohorts (Cohorts 1-6). Approximately 200 women with PPD 18 to 45 years of age will be screened to randomize up to 100 subjects across up to 6 cohorts. Approximately 10-30 subjects will be randomized into each cohort. Randomized subjects will receive **the investigational product (IP),** ganaxolone or **matching** placebo in a 1:1 ratio. In Cohorts 1-5 the **IP** will be administered intravenously over 60 hours. In Cohort 6 the **dosing** is initiated with **a 6-hour** intravenous (IV) infusion followed by oral **dosing** for **28** days **plus 3-day taper.**
Reason for Change: Updated details for Cohort 6			
11	Study Synopsis Study period (planned)	**Study period (planned):** March 2017 to December 2018	**Study period (planned):** March 2017 to **June 2019**
Reason for Change: Updated timeline estimate			

11	Study Synopsis Investigational product, dose, and mode of administration	**Cohort 6:** In this cohort treatment is initiated with an initial ganaxolone infusion followed by a transition to treatment with oral ganaxolone capsules for 14 days given at bedtime (QHS). The exact duration and dose of the infusion will be decided based on the results of previous cohorts. The first oral dose is administered following the IV dosing at 450 mg QHS. At subsequent days ganaxolone is administered at 675 mg QHS.	**Cohort 6:** In this cohort **dosing** is initiated with ganaxolone infusion **at a rate of 20 mg/h (40 ml/h of ganaxolone 0.5 mg/ml solution or matching placebo) for 6 hours** followed by ganaxolone **900 mg or matching placebo** capsules given **orally at dinner time for 28 days followed by a 3-day taper.**
Reason for Change: Updated details for Cohort 6			
12	Study Synopsis Methodology	In Cohort 6, following the screening period, there will be a 1-day inpatient treatment phase at a hospital or clinical pharmacology unit. The study drug will be administered intravenously over a period of ≤ 12 hours (exact dose and duration to be determined based on the results from previous cohorts), followed by administration of the first dose of the oral study drug (450 mg) at bedtime (HS). The subjects will be discharged home the next morning (Day 2), and oral dosing will be continued at home for 13 days (Days 2-14) at bedtime daily (QHS). There will be 2 safety follow-up visits after the last dose on post-treatment Weeks 1 and 4.	In Cohort 6, following the screening period, there will be a 1-day inpatient treatment phase at a hospital or clinical pharmacology unit. The study drug will be administered intravenously over a period of **6** hours followed by administration of the first dose of the oral study drug (**ganaxolone 900 mg or matching placebo**) at **dinner time.** The subjects will be discharged home the next morning (Day 2), and oral dosing will be continued at home for **27** days (Days 2-**28** at **dinner time** daily **followed by a 3-day taper.** There will be **3** safety follow-up visits after the last dose on post-treatment Weeks 1**, 4, and 6.**
Reason for Change: Updated details for Cohort 6			
12	Study Synopsis Inclusion Criteria	6. HAMD17 score of ≥ 26 at screening (HAMD17 must be ≥ 22 at Admission to the Unit on Day 0) 7. The diagnosis of PPD and severity of depression must be supported by the SAFER interview 8. Must agree to stop breastfeeding from start of study treatment to 45 days after infusion	6. HAMD17 score of ≥ 26 at screening (HAMD17 must be ≥ 22 **per CTNI rating** at Admission to the Unit on Day 0) 7. The diagnosis of PPD and severity of depression must be supported by the SAFER interview 8. Must agree to stop breastfeeding from start of study treatment to 45 days after **end of study treatment**
Reason for Change: Clarification of HAMD rating responsibility and breastfeeding timing			
13	Study Synopsis Pharmacokinetics	**Pharmacokinetics:** Six samples will be collected for pharmacokinetic analysis in Cohorts 1-5. Maximal plasma concentration (C_{max}), concentration at steady-state (C_{ss}, determined by the mean concentrations once steady-state is achieved by visual inspection), AUC_{0-24} (calculated as Css	**Pharmacokinetics:** Six samples will be collected for pharmacokinetic analysis in Cohorts 1-5 **and 12 samples in Cohort 6**. Maximal plasma concentration (C_{max}), concentration at steady-state (C_{ss}, determined by the mean concentrations once steady-state is achieved by visual inspection), AUC_{0-24} (calculated as C_{ss}

		multiplied by 24 hours) will be estimated. Four samples will be collected during the inpatient phase of Cohort 6 followed by collection of 2 samples during the outpatient phase during the study visits.	multiplied by 24 hours) will be estimated. **Seven** samples will be collected during the inpatient phase of Cohort 6 **(including 6 samples on Day 1)** followed by collection of 5 samples during the outpatient phase during the study visits **for a total of 12 samples in Cohort 6.**
Reason for Change: Updated details for Cohort 6			
13	Study Synopsis Statistical Methods	Primarily descriptive	**Sample size: No formal hypothesis testing will be performed, and the sample size is not based on statistical power considerations. A population of about 6 to 10 subjects per dose is commonly tested in studies which aim to establish a tolerability range for a new compound or a new formulation.** **Analysis Populations: The Screened Set will consist of all subjects who have signed an informed consent. The Randomized Set will consist of subjects randomized. The Safety Set will consist of all subjects who received IP. The modified Intent to Treat Set (mITT) will consist of all subjects in the Safety Set who have at least 1 post-baseline efficacy assessment. The Per-Protocol Set will consist of all subjects in the mITT set who do not have major protocol deviations that may affect key efficacy endpoints. The Infusion Completer Set will consist of all subjects in the Safety Set who completed the 60-hour infusion in Cohorts 1-5, and who completed the 6-hour infusion in Cohort 6. The Completer Set will consist of all subjects in the Safety Set who completed the 60-hour infusion and attended the final safety follow-up visit in Cohorts 1-5, and who completed the 6-hour infusion and oral dosing period and attended all outpatient visits including the safety follow-up visits in Cohort 6.** **Analysis Methods: Data analyses will primarily be descriptive. Continuous variables will be summarized as numbers of observations, means, measures of variance (e.g., standard deviation), and percentiles (e.g., median, minimum, maximum). Categorical variables will be summarized as numbers of observations and percentages. Results from exploratory statistical analyses of efficacy endpoints may be presented but only to aid in interpretation.**

Reason for Change: Added details for statistical analysis			
18	1.2.1.4 Preliminary safety information from the current trial (1042-PPD-2002)	Blank	**Cohort 3** **13 subjects in Cohort 3 have completed dosing as of September 5th, 2018 and respective data reviewed by the DRC. In this cohort ganaxolone (or matching placebo) was given as 12 mg IV bolus over 2 minutes followed by IV infusion at a rate of 12 mg/h for 48 hours after which the rate was lowered to 6 mg/h for the final 12 hours. The infusion was stopped at 60 hours. There have been no serious adverse events or adverse events leading to discontinuation, and no subject has needed a dose adjustment. The DRC has evaluated preliminary adverse event data from these 13 subjects and deemed this dosing regimen to be well-tolerated. The DRC has recommended that enrollment into Cohort 3 be completed with 20 subjects.**
Reason for Change: Added safety data from Cohort 3			
20	3.1 Study Design and Study Population	**In Cohort 6**, subjects randomized to ganaxolone will receive an initial IV infusion of ganaxolone followed by a transition to oral ganaxolone capsules administered at 450 mg QHS the first day and then at 675 mg QHS on Days 2-14. The exact duration and dose of the initial infusion will be decided based on the results of previous cohorts but will be less than 12 hours. Subjects randomized to placebo will receive an initial IV infusion of placebo followed by a transition to oral placebo capsules administered QHS for 14 days. Randomization will allocate subjects to the ganaxolone arm or placebo arm in 1:1 ratio.	**In Cohort 6**, subjects randomized to ganaxolone will receive an initial IV infusion of **20 mg/h (40 ml/h of** ganaxolone **0.5 mg/ml solution) for 6 hours** followed by **900 mg (4 capsules)** ganaxolone capsules administered **orally at dinner time for 28 days followed by a 3-day taper (3, 2, and 1 capsules per day, respectively).** Subjects randomized to placebo will receive an initial IV infusion of **matching** placebo **(at 40 ml/h)** followed by **4** placebo capsules administered **orally at dinner time for 28 days followed by a 3-day taper (3, 2, and 1 capsules per day, respectively).** Randomization will allocate subjects to the ganaxolone arm or placebo arm in 1:1 ratio.
Reason for Change: Updated details for Cohort 6			
21	3.3 Blinding Scheme	Subjects who are randomized to receive ganaxolone in Cohorts 1-5 will receive ganaxolone as an intravenous infusion for 60 hours with or without an intravenous ganaxolone bolus dose. Subjects who are randomized to placebo will receive placebo infusion for 60 hours (0.9% saline) with or without an intravenous placebo bolus	**Within cohorts, subjects will be randomized to ganaxolone or placebo in a 1:1 ratio. The randomization scheme will be prepared by an independent third-party vendor. Treatment assignments will be obtained by the investigator (or designee) via an Interactive Voice and/or Web Response System (IxRS).** Subjects who are

		dose. The placebo infusion is identical to ganaxolone in its appearance. In Cohort 6 subjects randomized to ganaxolone will receive an initial infusion of ganaxolone followed by a transition to treatment with oral ganaxolone capsules for 14 days. Subjects randomized to placebo will receive an initial infusion with IV placebo followed by a transition to treatment with oral placebo capsules for 14 days. The placebo infusion and placebo capsules are identical to the ganaxolone infusion and capsules in their appearance. An unblinded study pharmacist at the investigative site will prepare the ganaxolone and placebo IV solutions, and allocate capsule supply for Cohort 6. Persons involved in the evaluation of the study subjects (e.g. investigators, sub investigators, and physicians/nurses), will remain blinded at all times, except in case of an emergency. Subjects are blinded.	randomized to receive ganaxolone in Cohorts 1-5 will receive ganaxolone as an intravenous infusion for 60 hours with or without an intravenous ganaxolone bolus dose. Subjects who are randomized to placebo will receive **matching** placebo infusion for 60 hours (0.9% saline) with or without **a matching** intravenous placebo bolus dose. The placebo infusion is identical to ganaxolone in its appearance. In Cohort 6, subjects randomized to ganaxolone will receive an initial infusion of **20 mg/h (40 ml/h of** ganaxolone **0.5 mg/ml solution) for 6 hours** followed by treatment with oral **doses of 900 mg** ganaxolone **(4 capsules per dose) for 28 days followed by a 3-day taper (3, 2, and 1 capsules per day, respectively).** Subjects randomized to placebo will receive an initial infusion with **matching** IV placebo **(at 40 ml/hr)** followed by **matching** oral placebo **(4 capsules per dose) for 28 days followed by a 3-day taper (3, 2, and 1 capsules per day, respectively).** The placebo infusion and placebo capsules are identical to the ganaxolone infusion and **ganaxolone** capsules, **respectively**, in their appearance. An unblinded study pharmacist at the investigative site will prepare the ganaxolone and placebo IV solutions and allocate capsule supply for Cohort 6. **Members of the DRC will be unblinded at scheduled DRC meetings. All other study personnel, including persons** involved in the evaluation of the study subjects (e.g. investigators, sub-investigators, and physicians/nurses), will remain blinded at all times, except in case of an emergency. Subjects **will be** blinded.
Reason for Change: Updated details for Cohort 6			
23	3.4.5 Cohort 6	For Cohort 6, the infusion rate for the initial infusion on Day 1 will be decided based on the results of the previous cohorts. The goal of initiation of treatment with IV infusion followed by transition to oral capsules is to maximize the speed of onset of antidepressant activity while providing the convenience of oral dosing for the remainder of the treatment period. Under this IV-oral dosing schedule there may not be a need for a prolonged inpatient observation.	**For Cohort 6, the goal of initiation of treatment with IV infusion followed by oral capsules is to maximize the speed of onset of antidepressant activity while providing the convenience of oral dosing for the remainder of the treatment period. Under this IV-oral dosing schedule there may not be a need for a prolonged inpatient observation.** **This initial infusion is targeted to provide a fast onset of antidepressant activity by delivery of rapid plasma exposures to ganaxolone. At dinner time of Day 1 the**

		This initial infusion is targeted to provide a fast onset of antidepressant activity by delivery of rapid plasma exposures to ganaxolone. At bedtime of Day 1 the patient will take their first oral dose of ganaxolone of 450 mg (2 capsules). This dose is expected to provide mean Cmax plasma concentrations of approximately 150 ng/ml, which may be mildly sedating. In previous studies ganaxolone has been given up to a daily dose of 2000 mg, and at single doses of 1000 mg. Based on the previous experience this dose is expected to be safe. At subsequent nights (Days 2-14), the target dose is 675 mg (3 capsules) QHS. However, based on the assessment of the investigator the dose may be maintained at 450 mg in case of adverse events, such as grogginess in the morning. The mechanism by which ganaxolone is postulated to be efficacious under this dosing regimen is restructuring of sleep architecture.[2] Preclinical studies have shown that allopregnanolone has the capacity to modulate sleep, and disturbed sleep architecture is one of the hallmarks of depression.	**subjects will take their first oral dose of ganaxolone 900 mg or matching placebo (4 capsules). This dose is expected to provide mean C_{max} plasma concentrations of approximately 250-300 ng/mL and mean steady-state levels between 90 and 150 ng/mL, which may be mildly sedating. In previous studies ganaxolone has been given up to a daily dose of 2000 mg, and at single doses of 1000 mg. Based on the previous experience this dose is expected to be safe.** **At subsequent nights (Days 2-28), the target dose is ganaxolone 900 mg or matching placebo (4 capsules) at dinner time followed by a 3-day taper (3, 2, and 1 capsule/s per day, respectively). However, based on the assessment of the investigator the dose may be maintained at 675 mg or 450 mg (or matching placebo) in case of adverse events, such as grogginess in the morning. In the case of 3 capsules per day on day 28 the taper will consist of 2, 2, and 1 capsule/s on days 29, 30, and 31, respectively. In the case of 2 capsules per day on day 28 the taper will consist of 1 capsule on days 29, 30, and 31. If the subject cannot tolerate 450 mg (or matching placebo) per dose the investigator will contact the Medical Monitor to discuss dosing options.** **Subjects will be provided with a diary to capture the details of dose administration and associated food intake throughout the treatment period. Subjects will document the number of capsules taken and whether a fatty meal/snack (e.g., fatty yogurt, nuts, avocado) was consumed ±15 minutes of taking the capsules.** **The mechanism by which ganaxolone is postulated to be efficacious under this dosing regimen is restructuring of sleep architecture.[2] Preclinical studies have shown that allopregnanolone has the capacity to modulate sleep, and disturbed sleep architecture is one of the hallmarks of depression.**
Reason for Change: Updated details for Cohort 6			

24	3.5 Justification for Placebo as a Control Group	The Cohort 6 treatment period is initiated in an inpatient setting, which allows observation of the effects of the IV infusion and first dose effects of the oral medication during the approximately 24-hour stay on the unit.	The Cohort 6 treatment period is initiated in an inpatient setting, which allows observation of the effects of the IV infusion and first dose effects of the oral medication during the approximately **48**-hour stay on the unit.
Reason for Change: Updated details for Cohort 6			
24	3.6 Study Duration	For Cohort 6 there will be an initial infusion treatment during the approximately 24-hour inpatient treatment phase followed by 13 days of treatment as outpatient. There will be 2 safety follow-up visits after the outpatient treatment period on post-treatment Weeks 1 and 4. The total duration of the study will be up to 9 weeks for subjects participating in Cohort 6.	For Cohort 6 there will be an initial infusion treatment **and oral dose** during the approximately 24-hour inpatient **dosing** phase followed by **27** days of **oral** treatment as outpatient. There will be **3** safety follow-up visits after the outpatient treatment period on post-treatment Weeks **1,4, and 6.** The total duration of the study will be up to **12** weeks for subjects participating in Cohort 6.
Reason for Change: Updated details for Cohort 6			
24	3.7 Interim Analyses	In addition, safety and efficacy data from each cohort will be unblinded, and an analysis will be conducted for the purpose of dose selection for the next cohort. The dose for the next cohort will be decided based on these interim data analyses. The decision how to adjust the dose and/or the duration of the infusion will be made based on recommendations by a Data Review Committee (DRC) composed of the sponsor's Chief Medical Officer, and at least 2 other external physicians. At least one of the members will have special expertise in the clinical care of women with depression or postpartum depression. One of the members will have expertise in the conduct of clinical trials or analysis of clinical trial data.	In addition, safety and efficacy data from each cohort will be unblinded, and **analyses** will be conducted for the purpose of dose selection for the next cohort. The dose for the next cohort will be decided based on these interim data analyses. The decision how to adjust the dose and/or the duration of the infusion will be made based on recommendations by a Data Review Committee (DRC) composed of the sponsor's Chief Medical Officer, and at least 2 other external physicians. At least one of the members will have special expertise in the clinical care of women with depression or postpartum depression. One of the members will have expertise in the conduct of clinical trials or analysis of clinical trial data. **The study team and all parties other than the DRC will remain blinded.**
Reason for Change: Clarification on the Interim Analysis			
25	3.8 Definition of Completion	The Study Completion Date is defined as the date the final subject, across all sites, completes her final protocol-defined assessment for the final cohort. Please note that this includes all follow-up visits.	**A cohort is considered complete when the final subject in the cohort has completed the final protocol-defined assessment, including follow-up visits, for the cohort.** The Study Completion Date is defined as the date the final subject, across all sites, completes her final protocol-defined assessment**, including follow-up visits,** for the final cohort.
Reason for Change: Clarification of study completion			

26	4.1 Inclusion Criteria	6. HAMD17 score of ≥ 26 at screening (HAMD17 must be ≥ 22 at Admission to the Unit on Day 0) 7. The diagnosis of PPD and severity of depression must be supported by the SAFER interview 8. Must agree to stop breastfeeding from start of study treatment to 45 days after infusion	6. HAMD17 score of ≥ 26 at screening (HAMD17 must be ≥ 22 **per CTNI rating** at Admission to the Unit on Day 0) 7. The diagnosis of PPD and severity of depression must be supported by the SAFER interview 8. Must agree to stop breastfeeding from start of study treatment to 45 days after **end of study treatment**
Reason for Change: Clarification of HAMD rating responsibility and breastfeeding timing			
28	4.4 Discontinuation of Subjects	The investigator is encouraged to discuss withdrawal of a subject from the investigational product with the medical monitor when possible. If the investigational product is discontinued, regardless of the reason, the evaluations listed for Day 4 are to be performed as completely as possible for Cohort 1-5, and Day 14 evaluations for Cohort 6.	The investigator is encouraged to discuss withdrawal of a subject from the investigational product with the medical monitor when possible. **Withdrawn subjects who have not received IP will be replaced.** If the investigational product is discontinued, regardless of the reason, the evaluations listed for Day 4 are to be performed as completely as possible for Cohort 1-5, and Day **28** evaluations for Cohort 6.
Reason for Change: Clarification on discontinuation of subjects			
30	5.0 PRIOR AND CONCOMITANT TREATMENT	All non-study treatments (including herbal treatments and vitamins) received within 30 days prior to the screening visit (Visit 1) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate eCRF page.	All non-study treatments (including herbal treatments, vitamins**, and non-pharmacological treatments)** received within **60** days prior to the screening visit (Visit 1) and through the final study contact (including protocol-defined follow-up period) must be recorded on the appropriate eCRF page.
Reason for Change: Clarification on concomitant treatments and timing for data collection			
30	5.3 Concomitant Psychological Treatment	Concomitant psychological treatment refers to all psychological care the patient is receiving at the time of the screening visit. Concomitant psychological treatment information must be recorded on the concomitant psychological treatments eCRF page.	Concomitant psychological treatment refers to all psychological care the **subject** is receiving **between** the screening visit **and the end of the follow-up period regardless of the start date of the concomitant psychological treatment.** Concomitant psychological treatment information must be recorded on the concomitant psychological treatments eCRF page.
Reason for Change: Clarification of the timing for collection of psychological treatment			
31	5.3.1.3 Other Permitted Treatments	After the subject is discharged from the unit, any changes to the antidepressant or antianxiety medication regimen are not prohibited, but investigators are encouraged to maintain such drugs at stable doses if possible. Any changes	After the subject **completes** the **study treatment period**, any changes to the antidepressant or antianxiety medication regimen are not prohibited, but investigators are encouraged to maintain such drugs at stable doses if possible. Any changes in the

		in the medication regimen must be recorded on the concomitant medication eCRF page.	medication regimen must be recorded on the concomitant medication eCRF page.
Reason for Change: Clarification on the timing for permitted treatments			
31	5.3.2 Prohibited Treatments	The following classes of medications and treatments are prohibited during the inpatient study period.	The following classes of medications and treatments are prohibited during the study **treatment** period.
Reason for Change: Clarification on the timing for prohibited treatments			
33	6.2 Administration of Investigational Product(s)	For administration of the IV investigational product and IV placebo the investigator needs to use the Sponsor-approved Captisol®-compatible intravenous infusion bags and infusion sets which are prepared according to the Pharmacy manual. Any substitutions and deviations from the Pharmacy manual need to be approved by the sponsor. Ganaxolone oral capsules (Cohort 6 only) will be administered orally with food. Ganaxolone should be taken just before or together with a meal or snack and with 240 mL (8 oz) of water at bedtime.	For administration of the IV investigational product **(IP; ganaxolone or matching** placebo **[0.9% saline solution])** the investigator needs to use the Sponsor-approved Captisol®-compatible intravenous infusion bags and infusion sets which are prepared according to the Pharmacy manual. Any substitutions and deviations from the Pharmacy manual need to be approved by the sponsor. Ganaxolone **or matching placebo** capsules (Cohort 6 only) will be administered orally with food. Ganaxolone **or matching placebo capsules** should be taken **±15 minutes of a fatty meal or snack (e.g., fatty yogurt, nuts, avocado)** and with 240 mL (8 oz) of water at **dinner time.** **Subjects will be provided with a diary to capture the details of dose administration and associated food intake throughout the treatment period. Subjects will document the number of capsules taken and whether a fatty meal/snack (e.g., fatty yogurt, nuts, avocado) was consumed ±15 minutes of taking the capsules.**
Reason for Change: Updated details for Cohort 6			
34	6.2.1 Interactive Voice/Web Response System (IxRS) Technology for Investigational Product Management	The name and address of the IVRS/Interactive Web Response System (IWRS) for this study will be maintained in the Investigator's files at each study site. Interactive response technology will be used for the following investigational product tasks: • Randomization	The name and address of the Interactive **Voice**/Web Response System (**IxRS**) for this study will be maintained in the Investigator's files at each study site. Interactive response technology will be used for the following investigational product tasks: • Randomization • **Communication of treatment assignment to sites**
Reason for Change: Clarification of IxRS management			

34	6.2.2 Allocation of Subjects to IP	This is a double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule. Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined. After being randomized a patient will be replaced only if she discontinues prior to receiving study treatment.	This is a double-blind, placebo-controlled study. The actual **IP** given to individual subjects is determined by a randomization schedule **prepared by an independent third-party vendor. Within cohorts, subjects will be randomized to ganaxolone or placebo in a 1:1 ratio.** Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation. The randomization number represents a unique number corresponding to **IP kit number** allocated to the subject, once eligibility has been determined. After being randomized a **subject** will be replaced only if she discontinues prior to receiving **IP. The replacement subject will receive the same IP assignment as the replaced subject.**
Reason for Change: Clarification on allocation and replacement of subjects			
35	6.2.3 Dosing	Subjects entering the study will be randomized to ganaxolone or placebo at the Baseline Visit. The goal of Cohort 1 is to determine safety, tolerability, PK and efficacy of the IV formulation of ganaxolone in PPD subjects administered at a predicted dose mimicking the levels of allopregnanolone at the end of pregnancy, or higher.	Subjects entering the study will be randomized to ganaxolone or **matching** placebo at the Baseline Visit. The goal of **Cohorts 1-6** is to determine safety, tolerability, PK and efficacy of the IV **formulation (and in Cohort 6, the IV formulation followed by oral formulation)** of ganaxolone in PPD subjects administered at a predicted dose **regimen** mimicking the levels of allopregnanolone at the end of pregnancy, or higher.[10, 5, 14] **Infusion rates for ganaxolone IV will be the same as for placebo IV.**
Reason for Change: Updated details for Cohort 6			
35	6.2.3 Cohort 6	The rate and duration for the initial ganaxolone infusion will be decided based on the previous results. However, the duration of the infusion will not exceed 12 hours. Following completion of the infusion the patient will be administered a 450 mg dose (2 caps) of ganaxolone at bedtime (Day 1). On subsequent nights (Day 2-14) the patient will take 675 mg of ganaxolone QHS (unless the dose is adjusted as per the instructions from the investigator).	**For Cohort 6, an initial IV infusion 20 mg/h (40 ml/h of ganaxolone 0.5 mg/ml solution or matching placebo) for 6 hours will be followed by oral dose of 900 mg ganaxolone or matching placebo (4 capsules) at dinner time (Day 1). On subsequent nights (Day 2-28) the subject will take 900 mg of ganaxolone, or matching placebo (4 capsules), at dinner time followed by a 3-day taper (3, 2, and 1 capsule/s per day, respectively (unless the dose is adjusted as per the instructions from the investigator in which case the taper follows instructions in section 3.4.6).**

Reason for Change: Updated details for Cohort 6			
36	6.2.4 Dose Adjustments	The dose of the oral medication in Cohort 6 may be adjusted by lowering the dose from 675 mg QHS to 450 mg QHS if the patient experiences adverse effects, such as sedation in the morning. If the dose is adjusted, this must be recorded in the eCRF. Other dosing adjustments may be possible but they should be discussed with the medical monitor.	The dose of the oral medication in Cohort 6 may be adjusted by lowering the dose from **900 mg to** 675 mg **or** 450 mg**, or matching placebo at dinner time** if the **subject** experiences adverse effects, such as sedation in the morning. If the dose is adjusted, this must be recorded in the eCRF. Other dosing adjustments may be possible, but they should be discussed with the medical monitor.
Reason for Change: Updated details for Cohort 6			
37	6.3.1 Labeling	The site pharmacy will prepare the IV bags, which will include at minimum the subject ID, protocol number, and time and date of IV bag preparation. No information should be visible to the subject or staff, which could potentially unblind the study drug, or allude to the contents of the IV bag (e.g. “drug lot number”). Further details are provided in the pharmacy manual.	The site pharmacy will prepare the IV bags, which will include at minimum the subject ID, protocol number, and time and date of IV bag preparation. No information which could potentially unblind the study drug **should be visible to the subject or staff, and no packaging information should** allude to the contents of the IV bag (e.g., “drug lot number”). Further details are provided in the pharmacy manual.
Reason for Change: Clarification of IV bag labeling			
37	6.3.2.2 Ganaxolone and placebo oral capsules	The site pharmacy or delegated site staff will be responsible for dispensing the study treatment to the subject. Sufficient amount of capsules will be provided to the patient until the next study visit. Detailed instructions when to take the medication and a reminder to take the study medication with food (with a meal or snack) at bedtime and with 240 mL (8 oz) of water will be provided to the patient.	The site pharmacy or delegated site staff will be responsible for dispensing the study treatment to the subject. **A sufficient number** of capsules will be provided to the **subject** until the next study visit **plus at least 3-day overage.** Detailed instructions when to take the medication and a reminder to take the study medication with **fatty** food (meal or snack, **e.g., fatty yogurt, nuts, avocado) at dinner time** and with 240 mL (8 oz) of water will be provided to the **subject along with a medication diary to document intake of IP and fatty meal/snack ±15 minutes.**
Reason for Change: Updated details for Cohort 6			
39	6.5.1 Administration of IV ganaxoloneIP (Cohorts 1-6)	The study drug will be administered IV via an indwelling catheter inserted in a vein on the arm or hand. The study drug should be infused as instructed throughout the study period. If the study drug is stopped temporarily (e.g. catheter change) the infusion may be re-started at the same rate as before. A new infusion bag should be prepared every 24 hours. The catheter should be flushed with saline at the same time when the tubing is changed. The	The **IP** will be administered IV via an indwelling catheter inserted in a vein on the arm or hand. The **IP** should be **given as continuous infusion** as instructed. If the study drug is stopped temporarily (e.g. catheter change) the infusion may be re-started at the same rate as before. A new infusion bag should be prepared every 24 hours. The catheter should be flushed with saline at the same time when the tubing is changed. The catheter site should be inspected for inflammation at least twice a

		catheter site should be inspected for inflammation at least twice a day. For details please see pharmacy manual.	day. For details please see pharmacy manual.
Reason for Change: Clarification of administration of IV			
39	6.5.2 Administration of oral ganaxolone or placebo capsules (Cohort 6)	Oral doses of ganaxolone should be taken at bedtime with food (just before or with a meal or snack) and with 240 mL (8 oz) of water at home.	Oral doses of ganaxolone **or matching placebo** should be taken at **dinner time** with **fatty** food **(±15 minutes of a fatty** meal or snack**, e.g., fatty yogurt, nuts, avocado**) and with 240 mL (8 oz) of water at home.
Reason for Change: Clarification of oral dosing			
40	7.0 STUDY PROCEDURES	In Cohort 6 the treatment is initiated with an intravenous (IV) infusion followed by a transition to oral ganaxolone. Additional patients may be included into these cohorts or additional cohorts may be added, but will not exceed 100 randomized subjects for the study. The screening period for each cohort will be up to 2 weeks. Following the screening period, there will be a 4-day inpatient treatment phase at a hospital or clinical pharmacology unit for Cohorts 1-5 during which a 60-hour infusion of ganaxolone or placebo will be administered (with or without bolus dosing). The subjects will be discharged from the unit on the morning of Day 4. There will be 2 safety follow-up visits after inpatient discharge on post-treatment Weeks 1 and 4. In Cohort 6, following the screening period, there will be a 1-day inpatient treatment phase at a hospital or clinical pharmacology unit during which an infusion of ganaxolone or placebo will be administered initially before oral dosing is started. The subjects will be admitted in the morning of Day 1 (infusion day) and discharged from the unit in the morning of Day 2. The first dose of oral ganaxolone (2 capsules; 450 mg) will be administered following the infusion at bedtime (HS) of Day 1. Oral dosing is continued as outpatient on Days 2-14. The dosing regimen during the outpatient phase of Cohort 6 is 675 (3 capsules) mg at bedtime daily (QHS). There will be 2 safety follow-up visits after the last dose on post-	In Cohort 6 the treatment is initiated with **a 6-hour** intravenous (IV) infusion followed by oral ganaxolone **or matching placebo.** Additional **subjects** may be included into these cohorts or additional cohorts may be added, but will not exceed 100 randomized subjects for the study. The screening period for each cohort will be up to 2 weeks. Following the screening period, there will be a 4-day inpatient treatment phase at a hospital or clinical pharmacology unit for Cohorts 1-5 during which a 60-hour infusion of ganaxolone or placebo will be administered (with or without bolus dosing). The subjects will be discharged from the unit on the morning of Day 4. There will be 2 safety follow-up visits after inpatient discharge on post-treatment Weeks 1 and 4. In Cohort 6, following the screening period, there will be a 1-day inpatient treatment phase at a hospital or clinical pharmacology unit during which **a 6-hour** infusion of ganaxolone or **matching** placebo will be administered initially **from 9 am to 3 pm (±1 hour)** before oral dosing is started **at 7 pm (±1 hour).** The subjects will be admitted **on** Day 0 and discharged from the unit in the morning of Day 2. The first dose of oral ganaxolone (4 capsules; **900** mg) **or matching placebo** will be administered **at dinner time (around 7 pm**) of Day 1, **4 hours after the end of infusion on Day 1.** Oral dosing is continued as outpatient on Days 2-**28**. The dosing regimen during the outpatient phase of Cohort 6 is **900 mg or placebo (4** capsules) at **dinner time** daily**. A 3-day taper will follow at days 29, 30, and 31, as described in Section 3.4.6.** There will be **3** safety follow-up visits after the last dose on post-treatment Weeks 1**,4,**

		treatment Weeks 1 and 4. Following the analysis of the data from the first 10 subjects in Cohort 6, the Data Review Committee may recommend that after completion of the infusion of the study drug on Day 1 the subjects can be discharged home based on the assessment of the investigator, and the subjects begin taking the oral doses of the study medication at home. The subjects will take a 450 mg dose (2 caps) on Day 1 (QHS) and continue with the 675 mg dose on Days 2-14. Those subjects who are discharged home on Day 1 will come back for a study visit in the Morning of Day 2 (for Day 2 assessments; Table 3). Following completion of the Day 2 assessment they will continue the visit and assessment schedule as outlined in Table 2.	**and 6.** **On Day 1 subjects will have 6 PK samplings: at 1 hour after the end of the 6-hour infusion (i.e., at 4 pm), at 7 pm (just prior to the oral dosing), and at 1, 2, 3, and 4 hours post oral dosing (at 8, 9, 10, and 11 pm) as well at 8 am the following morning (on Day 2) prior to discharge.** The subjects will take a **900** mg dose **or placebo (4** caps) on **the evening of** Day 1 **at dinner time** and continue with the **900** mg dose **or matching placebo at dinner time** on Days 2**-28. A 3-day taper will follow as described in Section 3.4.6.**
Reason for Change: Updated details for Cohort 6			
47	7.5 Admission to the Unit and Infusion (Day +1) – Cohort 6 (Screening and Admission visits for Cohort 6 described in Section 7.1 and 7.2, respectively)	7.5.1 Before Infusion (Morning of Day +1; Baseline) • Admission to the unit. The patient arrives on the unit on the day of the infusion (Day +1) to complete assessments and accommodate to the unit. • Conduct HAMD17 interview • EPDS • STAI6 • Assess CGI-S • Review concomitant medications and therapies • Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate), • Collect ECG • Collect urine drug screen and urine pregnancy test • Collect safety laboratory tests • Collect neurosteroid level • Measure weight • Stanford Sleepiness Scale (SSS) • Conduct CSSRS interview • Collect AEs • Review inclusion and exclusion criteria (including hematology and chemistry from the screening visit); HAMD17 must be ≥ 22 for randomization.	**7.5.1 Before Infusion (Morning of Day +1; Baseline)** • **CTNI to conduct HAMD17 interview** • **EPDS** • **STAI6** • **Assess CGI-S** • **Review concomitant medications** • **Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate),** • **Stanford Sleepiness Scale (SSS)** • **Conduct CSSRS interview** • **Collect AEs** • **Randomization** • **The subject's bed should be placed close to the nursing station in an area that allows visual observation of the subject** • **Start monitoring of pulse oximetry** **7.5.2 During the Infusion and Evening of Day +1 (Day +1)** • **Start 6-hour infusion at 40 mL/hr at 9 am of Day +1 (0h) after baseline assessments are completed (listed above)** • **End 6-hour infusion** • **Complete +6h assessments after the end of the 6-hour infusion CTNI to**

		• Randomization • The patient's bed should be placed close to the nursing station in an area that allows visual observation of the patient throughout the infusion period. • Start monitoring of pulse oximetry • Start Q15 minutes health checks (e.g. to observe general wellbeing and behavior, monitor infusion) • If the patient is breastfeeding, she is encouraged to "pump and dump" while inpatient and for 45 days after the end of the outpatient study period. She should be provided with a breast pump. 7.5.2 During the Infusion and Evening of Day +1(Day +1) • Start infusion in the early afternoon of Day +1 (0h) after baseline assessments are completed (listed above) • Conduct interviews for HAMD17 (+6h) • Conduct interviews for CGI-I (+6h) • EPDS (+6h) • STAI6 (+6) • Collect AEs • Collect ECG (+6h) • Collect VS (BP, pulse, respiratory rate, pulse oximetry, temperature): (+6h) • Collect SSS (+6h) • Collect a pharmacokinetic sample (+6h; before the infusion is turned off) • Collect neurosteroid level (+6h) • Record concomitant medications • Conduct CSSRS interview (+6h) • Stop the infusion after all +6h assessments have been completed • Collect a pharmacokinetic sample before administration of the oral study drug • Administer 450 mg of ganaxolone at bedtime with a snack (two 225 mg capsules or two placebo capsules) • Collect a pharmacokinetic sample 1 hour after taking the oral dose	**conduct interviews for HAMD17 (+6h)** **• Conduct interviews for CGI-I (+6h)** **• EPDS (+6h)** **• STAI6 (+6h)** **• Collect AEs** **• Collect ECG (+6h)** **• Collect VS (BP, pulse, respiratory rate, pulse oximetry, temperature): (+6h)** **• Collect SSS (+6h)** **• Collect pharmacokinetic samples (+7h [i.e., 1 hour after the end of the infusion], at +10h [i.e., just before the oral dose], and at 1, 2, 3, and 4 hours after the oral dose** **• Collect neurosteroid level (+6h)** **• Record concomitant medications** **• Conduct CSSRS interview (+6h)** **• Administer the IP: 900 mg of ganaxolone, or matching placebo (four 225 mg capsules or four placebo capsules), at dinner time (i.e., at 7 pm) ±15 minutes of a fatty meal or snack (e.g., fatty yogurt, nuts, avocado)** **• Continue monitoring of pulse oximetry and Q15 min health checks** **7.5.3 Day + 2 (Discharge and transition to outpatient treatment)** **• The assessments listed below are completed before discharge** **• CTNI to conduct interviews for HAMD17** **• Conduct interviews for CGI-I** **• EPDS** **• STAI6** **• Collect AEs** **• Collect ECG** **• Collect VS (BP, pulse, respiratory rate, pulse oximetry, temperature)** **• Collect SSS** **• Collect a pharmacokinetic sample at 8 am (23h)** **• Collect neurosteroid level** **• Record concomitant medications** **• Conduct CSSRS interview** **• Perform physical examination** **• Dispense medication bottle** **• Provide the subject with dosing instructions and subject diary completion.** **• Subject will take the IP (900 mg dose of ganaxolone, or matching placebo) at dinner time (four 225 mg capsules, or**

		• Continue monitoring of pulse oximetry and Q15 min health checks 7.5.3 Day + 2 (Discharge and transition to outpatient treatment) • The assessments listed below are completed before discharge • Conduct interviews for HAMD17 • Conduct interviews for CGI-I • EPDS • STAI6 • Collect AEs • Collect ECG • Collect VS (BP, pulse, respiratory rate, pulse oximetry, temperature) • Collect SSS • Collect a pharmacokinetic sample • Collect neurosteroid level • Record concomitant medications • Conduct CSSRS interview • Dispense outpatient medication supply • Patient will take a 675 mg dose of ganaxolone at bedtime (three 225 mg capsules) 7.6 Outpatient treatment phase (Days + 3 – +14) - Cohort 6 7.6.1 Safety phone calls (Days +3, +5, +9 and +11) • A safety phone call is made on days +3, +5, +9, and +11 by the PI (or the sub-I). The patient is asked about her general wellbeing. AEs are recorded. 7.6.2 Visit 3 (Day +7) • Conduct HAMD17 interview • EPDS • STAI6 • Assess CGI-I • Review concomitant medications and therapies • Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate), • Collect ECG • Collect urine drug screen and urine pregnancy test • Collect safety laboratory tests • Collect neurosteroid level • Collect a pharmacokinetic sample • Stanford Sleepiness Scale (SSS)	**matching placebo capsules)** **7.6 Outpatient treatment phase (Days + 3 – +29) - Cohort 6** **7.6.1 Safety phone calls (Days +3, +5, +10 and +13)** **• A safety phone call is made on days +3, +5, +10, and +13 by the PI (or the sub-I). The subject is asked about her general wellbeing. AEs are recorded.** **7.6.2 Visit 3 HAMD Call (Day +4 ±1 day)** **• CTNI to conduct HAMD17 interview** **7.6.3 Visit 4 (Day +8)** **• CTNI to conduct HAMD17 interview** **• EPDS** **• STAI6** **• Assess CGI-I** **• Review concomitant medications and therapies** **• Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate),** **• Collect ECG** **• Collect urine sample for urinalysis, drug screen and urine pregnancy test** **• Collect safety laboratory tests** **• Collect neurosteroid level** **• Collect a pharmacokinetic sample** **• Stanford Sleepiness Scale (SSS)** **• Conduct CSSRS interview** **• Collect AEs** **• Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions. IP return and accountability.** **• Subject will continue to take study drug (900 mg of ganaxolone, or matching placebo) at dinner time (unless the dose is lowered to 675 mg, or 450 mg, or matching placebo at dinner time as per instructions from the investigator)** **7.6.4 Visit 5 HAMD Call (Day +11 ±1 day)** **• CTNI to conduct HAMD17 interview** **7.6.5 Visit 6 (Day +15 ±2 days)**

		• Conduct CSSRS interview • Collect AEs • Dispense outpatient medication supply • Patient will continue to take 675 mg of ganaxolone QHS (unless the dose is lowered to 450 mg QHS as per instructions from the investigator) 7.6.3 Visit 4 (Day +14) • Conduct HAMD17 interview • EPDS • STAI6 • Assess CGI-I • Review concomitant medications and therapies • Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate), • Collect ECG • Collect urine drug screen and urine pregnancy test • Collect safety laboratory tests • Collect neurosteroid level • Collect a pharmacokinetic sample • Measure weight • Stanford Sleepiness Scale (SSS) • Conduct CSSRS interview • Collect AEs • Perform physical examination 7.7 Post–treatment Follow-up Period (Days +15 to +44) – Cohort 6 7.7.1 First Post-treatment Follow-up Visit - 7 days After the Last On-treatment Visit (Day +21) • The Follow-up Visit 1 should occur about 1 week after the Day 14 visit. • Conduct interviews for HAMD17 • Perform EPDS • Perform STAI6 • Assess CGI-I • Review concomitant medications and therapies • Collect vital signs (BP, pulse, temperature, RR) • Collect safety laboratory tests • Collect neurosteroid level • Collect urine drug screen and urine pregnancy test • Measure weight • Conduct CSSRS interview • Collect SSS • Collect AEs	**• CTNI to conduct HAMD17 interview • EPDS • STAI6 • Assess CGI-I • Review concomitant medications and therapies • Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate), • Collect ECG • Collect urine sample for urinalysis, drug screen and urine pregnancy test • Collect safety laboratory tests • Collect neurosteroid level • Collect a pharmacokinetic sample • Measure weight • Stanford Sleepiness Scale (SSS) • Conduct CSSRS interview • Collect AEs • Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or weekends). Provide the subject with dosing instructions. IP return and accountability. • Perform physical examination 7.6.6 Visit 7 (Day +22 ±3 days) • CTNI to conduct HAMD17 interview • EPDS • STAI6 • Assess CGI-I • Review concomitant medications and therapies • Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate), • Collect ECG • Collect urine sample for urinalysis, drug screen and urine pregnancy test • Collect neurosteroid level • Collect a pharmacokinetic sample • Stanford Sleepiness Scale (SSS) • Conduct CSSRS interview • Collect AEs • Dispense study medication with a supply to last until the next visit (+ 3 days overage to cover for unexpected need to re-schedule a study visit or**

		7.7.2 Second Post-treatment Follow-up Visit - 30 days After the Last On-treatment Visit (Day +44) • The Follow-up Visit 2 should occur about 30 days after the Day 14 visit. • Conduct interviews for HAMD17 • Perform EPDS • Perform STAI6 • Assess CGI-I • Review concomitant medications and therapies • Collect vital signs (BP, pulse, temperature, RR) • Collect urine drug screen and urine pregnancy test • Measure weight • Conduct CSSRS interview • Collect SSS • Collect AEs	**weekends). Provide the subject with dosing instructions. IP return and accountability.** **7.6.7 Visit 8 (Day +29 ±3 days)** **• CTNI to conduct HAMD17 interview** **• EPDS** **• STAI6** **• Assess CGI-I** **• Review concomitant medications and therapies** **• Collect vital signs (BP, pulse, temperature, pulse oximetry, respiratory rate),** **• Collect ECG** **• Collect urine sample for urinalysis, drug screen and urine pregnancy test** **• Collect safety laboratory tests** **• Collect a pharmacokinetic sample** **• Measure weight** **• Stanford Sleepiness Scale (SSS)** **• Conduct CSSRS interview** **• Collect AEs** **• Dispense study medication with a supply to last through the taper period. Provide the subject with dosing instructions. IP return and accountability.** **• Begin 3-day taper (3 capsules on Day 29, 2 capsules on Day30, 1 capsule on Day31, or, if Day 28 dose is other than ganaxolone 900 mg or placebo, follow instructions in section 3.4.6)** **• Perform physical examination** **7.7 Post–treatment Follow-up Period (Days +29 to +71) – Cohort 6** **7.7.1 First Post-treatment Follow-up Visit - 7 days After the Last On-treatment Visit (Day +36)** **• The Follow-up Visit 1 should occur about 1 week after the Day 29 visit.** **• CTNI to conduct interviews for HAMD17** **• Perform EPDS** **• Perform STAI6** **• Assess CGI-I** **• Review concomitant medications and therapies** **• Collect vital signs (BP, pulse, temperature, RR)** **• Collect ECG Collect neurosteroid level**

			• **Collect a pharmacokinetic sample** • **Collect urine sample for urinalysis, drug screen and urine pregnancy test** • **Measure weight** • **Conduct CSSRS interview** • **Collect SSS** • **Collect AEs** • **IP return and accountability** **7.7.2 Second Post-treatment Follow-up Visit - 28 days After the Last On-treatment Visit (Day +57)** • **The Follow-up Visit 2 should occur about 28 days after the Day 29 visit.** • **CTNI to conduct interviews for HAMD17** • **Perform EPDS** • **Perform STAI6** • **Assess CGI-I** • **Review concomitant medications and therapies** • **Collect vital signs (BP, pulse, temperature, RR)** • **Collect safety laboratory tests** • **Collect urine sample for urinalysis, drug screen and urine pregnancy test** • **Measure weight** • **Conduct CSSRS interview** • **Collect SSS** • **Collect AEs** **7.7.3 Third Post-treatment Follow-up Visit - 42 days After the Last On-treatment Visit (Day +71)** • **The Follow-up Visit 3 should occur about 42 days after the Day 29 visit.** • **CTNI to conduct interviews for HAMD17** • **Perform EPDS** • **Perform STAI6** • **Assess CGI-I** • **Review concomitant medications and therapies** • **Collect vital signs (BP, pulse, temperature, RR)** • **Collect urine sample for urinalysis, drug screen and urine pregnancy test** • **Measure weight** • **Conduct CSSRS interview** • **Collect SSS**

			• **Collect AEs**
Reason for Change: Updated details for Cohort 6			
54	Table 2 Schedule of Assessments – Cohort 6		Updated schedule based on details in section 7.5
Reason for Change: Updated details for Cohort 6			
56	7.8.5 Physical Examination	A complete physical examination will be performed at screening and before discharge from the unit.	A complete physical examination will be performed at screening, before discharge from the unit**, and during visits 6 and 8 (outpatient visits) of Cohort 6.**
Reason for Change: Updated details for Cohort 6			
59	7.8.6.2 The Hamilton Depression Rating Scale	The Hamilton Depression Rating Scale (HAMD) is a commonly-used semi-structured clinician-rated instrument which assess the range of symptoms that are most frequently observed in subjects with major depression. HAMD has undergone a considerable amount of psychometric study and is accepted as a valid standard of symptom outcome assessment in studies of major depression. In this study the symptoms of depression will be scored using the original 17-item HAMD scale (HAMD17). The 6 item version of this scale, known as HAMD6, will be derived from these data and used as an additional measure of changes in symptoms of depression. The items on the HAMD6 scale are as follows: depressed mood, work and interests, general somatic symptoms (tiredness), anxiety, guilt feelings, and psychomotor retardation. Both HAMD6 and HAMD17 have been validated and used in many clinical trials of antidepressant medications.[9] The use of the 6-item scale is justified because many items on the 17-item version cannot be expected to change over short period of time (e.g. weight or sleep).	The Hamilton Depression Rating Scale (HAMD) is a commonly-used semi-structured clinician-rated instrument which assess the range of symptoms that are most frequently observed in subjects with major depression. HAMD has undergone a considerable amount of psychometric study and is accepted as a valid standard of symptom outcome assessment in studies of major depression. In this study the symptoms of depression will be scored using the original 17-item HAMD scale (HAMD17). The 6-item version of this scale, known as HAMD6, will be derived from these data and used as an additional measure of changes in symptoms of depression. The items on the HAMD6 scale are as follows: depressed mood, work and interests, general somatic symptoms (tiredness), anxiety, guilt feelings, and psychomotor retardation. Both HAMD6 and HAMD17 have been validated and used in many clinical trials of antidepressant medications.[9] The use of the 6-item scale is justified because many items on the 17-item version cannot be expected to change over short period of time (e.g. weight or sleep). **All HAMD17 ratings, except the one done at screening, will be conducted by CTNI raters.**
Reason for Change: Clarification of HAMD17 rating responsibilities			

61	Table 4. Volume of Blood to Be Drawn from Each Subject (Cohort 6)		Updated to include additional volume of blood draws for Cohort 6
Reason for Change: Updated details for Cohort 6			
68	9.5 Statistical Analysis Plan	Statistical analyses will be mostly descriptive. The purpose of this study is to identify a ganaxolone dose and exposure level that is safe and well tolerated. Efficacy data will be collected but they are considered exploratory because of the small sample size. The SAP will provide the statistical methods and definitions for the analysis of the safety and efficacy data, and it will describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, or unused data will be addressed. The SAP will be finalized prior to completion of the first cohort to preserve the integrity of the statistical analysis and study conclusions.	**Data** analyses will **primarily** be descriptive. The purpose of this study is to identify a ganaxolone dose and exposure level that is safe and well tolerated. Efficacy data will be collected but **will be considered hypothesis-generating i.e., there are no *a priori* hypotheses on which the study was powered. Results from exploratory statistical analyses may be presented but only to aid in interpretation.** The SAP will provide the statistical methods and definitions for the analysis of the safety and efficacy data, and it will describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, or unused data will be addressed. The SAP will be finalized prior to completion of the first cohort to preserve the integrity of the statistical analysis and study conclusions. **This will not preclude amendments to the SAP before database lock.**
Reason for Change: Added details for statistical analysis			
68	9.5.1 Planned Interim Analysis	An interim unblinded analysis of safety and efficacy data will be conducted for each cohort. Based on these data the dose for the next cohort will be decided. The dose recommendation will be made by a Data Review Committee (DRC) comprised of the sponsor's Chief Medical Officer and 2 external physicians familiar with the clinical care of women with major depression or PPD and with experience in conducting clinical trials. A separate guidance document will outline the functions and membership of the DRC. The Marinus and the CRO study teams will remain blinded until the database lock of each cohort.	**Safety** and efficacy data **from each cohort will be unblinded, and analyses** will be conducted for the **purpose of** dose **selection for the next cohort. The dose** for the next cohort will be decided **based on these interim data analyses. The decision how to adjust the dose and/or the duration of the infusion** will be made **based on recommendations** by a Data Review Committee (DRC) **composed** of the sponsor's Chief Medical Officer, and **at least 2** other external physicians. **At least one of the members will have special expertise in the** clinical care of women with depression or **postpartum depression. One of the members will have expertise in the conduct of** clinical trials **or analysis of clinical trial data. The study team and**

			all parties other than the DRC will remain blinded. **The dose for the subsequent cohorts will be selected with the goal of gaining additional information on ganaxolone's tolerability and dose-response profile.** A separate **DRC** guidance document **outlines the principles for dose selection.** Marinus **may decide to stop** the study**, or make** the **data public, after completion of any** cohort.
Reason for Change: Clarification of planned interim analyses			
69	9.5.3 Study Population	The **Screened Set** will consist of all subjects who have signed an informed consent. The **Safety Set** will consist of all subjects who received ganaxolone. The **modified Intent to Treat Set** (mITT) will consist of all subjects in the Safety Set who have at least 1 post-randomization efficacy assessment. The **Per-Protocol Set** will consist of all subjects in the mITT set who do not have major protocol deviations that may affect key efficacy endpoints. The **Infusion Completer Set** will consist of all subjects in the Safety Set who completed the 60 hour infusion in Cohort 1-5, and who completed the initial infusion in Cohort 6. The **Completer Set** will consist of all subjects in the Safety Set who completed the 60 hour infusion and attended the final safety follow-up visit in Cohorts 1-5. In Cohort 6 the completer set will consist of subjects who completed the initial infusion and oral treatment period and attended all outpatient visits including the safety follow-up visits.	The **Screened Set** will consist of all subjects who have signed an informed consent. **The Randomized Set will consist of all subjects randomized.** The **Safety Set** will consist of all subjects who received **IP.** The **modified Intent to Treat Set** (mITT) will consist of all subjects in the Safety Set who have at least 1 post-randomization efficacy assessment. The **Per-Protocol Set** will consist of all subjects in the mITT set who do not have major protocol deviations that may affect key efficacy endpoints. The **Infusion Completer Set** will consist of all subjects in the Safety Set who completed the 60-hour infusion in Cohort 1-5, and who completed the initial infusion in Cohort 6. The **Completer Set** will consist of all subjects in the Safety Set who completed the 60-hour infusion and attended the final safety follow-up visit in Cohorts 1-5. In Cohort 6 the completer set will consist of subjects who completed the initial infusion and oral **IP dosing** period **with at least 80% oral dosing compliance** and attended all outpatient visits including the safety follow-up visits.
Reason for Change: Clarification of study population			
70	9.5.7 Safety Analyses	Reported AEs terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of Treatment Emergent AEs (TEAEs) will be summarized by treatment group, system organ class preferred terms, severity and	Reported **AE** terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of Treatment Emergent AEs (TEAEs**), defined as any AE that started or worsened after first administration of IP,** will be summarized by treatment group, system

		relatedness for each cohort. SAEs and AEs leading to discontinuation of the study drug will be summarized by treatment group for each cohort. The absolute values and change from baseline in laboratory tests, vital signs, SSS, ECGs and CSSRS will be summarized by treatment group for each cohort. Potentially clinically important findings will be summarized or listed.	organ class preferred terms, severity and relatedness for each cohort. SAEs and AEs leading to discontinuation of the study drug will be **listed separately** for each cohort. The absolute values and change from baseline in laboratory tests, vital signs, SSS, ECGs and CSSRS will be summarized by treatment group for each cohort. Potentially clinically important findings will be **included in AE summaries and listings.**
Reason for Change: Clarification of safety analyses			
70	9.5.8 Efficacy Analyses	Data for efficacy-related variables (e.g. HAMD17, HAMD6, STAI6, EPDS) will be summarized by visit and by change from baseline. Items related to sleep and anxiety within the HAMD17 and EPDS scales may be tabulated separately.	**9.5.8.1 Primary Endpoint** **The primary efficacy endpoint will be HAMD17 total score change from baseline to 60 hours post-infusion (on Day 3) for Cohorts 1-3 and to Day 29 for Cohort 6. The primary analysis in each cohort will be done using the mITT set. Although the trial is not powered for inferential analysis and there is no consideration for control of type 1 error across multiple cohorts, a clinically meaningful numeric difference in means of 3-4 points between ganaxalone and placebo treatment groups would be considered an indication of efficacy and will be the most influential outcome in the overall assessment of the efficacy of ganaxalone in treating PPD.** **9.5.8.2 Secondary Endpoints** **The trial will also evaluate the following secondary endpoints at each post-baseline data collection time point to provide additional evidence of the efficacy of ganaxalone in treating PPD:** • **Change from baseline in HAMD17 total score other than at 60 hours post-infusion (on Day 3) for Cohorts 1-3 and to Day 29 for Cohort 6** • **HAMD17 response defined as at least a 50% reduction from baseline in total score** • **HAMD17 remission defined as total score <= 7** • **Change from baseline in EPDS total score** • **Change from baseline in STAI6** • **CGI-I**

9.5.8.3 Exploratory Endpoints

[redacted]

9.5.8.4 Statistical Methods

[redacted]

			[redacted]
Reason for Change: Clarification of efficacy analysis			
71	9.5.10 Pharmacokinetic Analyses	The following pharmacokinetics parameters will be estimated for each subject receiving ganaxolone, if sufficient data are available: Maximal plasma concentration (C_{max}), concentration at steady-state (C_{ss}, determined by the mean concentrations once steady-state is achieved by visual inspection), AUC_{0-24} (calculated as Css multiplied by 24 hours). PK samples will be collected from subjects participating in Cohort 6 during the IV and oral dosing portion of the study.	The following pharmacokinetics parameters will be estimated for each subject receiving ganaxolone, if sufficient data are available: Maximal plasma concentration (C_{max}), concentration at steady-state (C_{ss}, determined by the mean concentrations once steady-state is achieved by visual inspection), AUC_{0-24} (calculated as C_{ss} multiplied by 24 hours). PK samples will be collected from subjects participating in Cohort 6 **after the IV infusion, before and** during the oral dosing portion of the study.
Reason for Change: Updated PK sampling and timing			
77	11.0 REFERENCES	Blank	**16. Helmreich I, Wagner S, Mergl R, et al. Sensitivity to changes during antidepressant treatment: a comparison of unidimensional subscales of the Inventory of Depressive Symptomatology (IDS-C) and the Hamilton Depression Rating Scale (HAMD) in patients with mild major, minor or subsyndromal depression. Eur Arch Psychiatry Clin Neurosci. 2012 Jun;262(4):291-304** **17. Boessen R1, Groenwold RH, Knol MJ, et al. Comparing HAMD(17) and HAMD subscales on their ability to differentiate active treatment from placebo in randomized controlled trials. J Affect Disord. 2013 Mar 5;145(3):363-9.** **18. Thase ME, Chen D, Edwards J, Ruth A. Efficacy of vilazodone on anxiety symptoms in patients with major depressive disorder. Int Clin Psychopharmacol. 2014 Nov;29(6):351-6.**
Reason for Change: Added references			

Additional grammatical, typographical errors and formatting revisions have been made in the document but are not identified here.