Statistical Analysis Plan

Sponsor:	Marinus Pharmaceuticals
Protocol No:	1042-PPD-2002
PRA Project Id:	MRSGNXLN-GNXLNE
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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
CRF Version No./Date:	2.0 / 09AUG2018
SAP No.	3.1 (Amendment to 2.0)

1.0 Approvals

Sponsors	
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2.0 Purpose

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Marinus Pharmaceuticals Protocol 1042-PPD-2002.

3.0 Scope

This SAP was first created during the trial start-up and, per protocol, was signed off by the Sponsor prior to completion of the first cohort of the trial. The SAP can be amended, as needed, up to unblinding. Each amendment must be approved and signed off by Sponsor. If an amendment to the SAP requires updates to analysis data set or TFL (table, figure and listing) programming, the amendment must be signed off by the Sponsor prior to programming changes being made.

4.0 Introduction

This SAP should be read in conjunction with the study protocol and case report form (CRF). This SAP amendment is based on Protocol Version 8.0, Amendment 7 dated 08Oct2018 and CRF dated 09Aug2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Analyses presented to the Data Review Committee (DRC), as well as the pharmacokinetic (PK) and neurosteroid analyses, will not be detailed in this SAP.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified in Section 4.1. Any post-hoc or unplanned analyses not included in this SAP, or significant changes from the planned analysis in this SAP, will be clearly identified in Section 9.8.2 of the clinical study report (CSR). Changes to planned analyses after database lock do not require an updated SAP but should be included in the CSR.

4.1 Changes from Protocol

- Protocol Synopsis and Sections 2.2.1 and 7.8.7: Change from baseline analysis for the Columbia-Suicide Severity Rating Scale (C-SSRS) will not be performed. Instead, the number of subjects who answered “yes” to the 5 suicidal ideation questions and the 5 suicidal behavior questions of the C-SSRS will be tabulated.
- Protocol Synopsis and Section 2.2.1: Change from baseline analysis for physical examinations will be performed. Details of the physical examination will be listed only.
- Section 9.5.3: The Per Protocol Set will consist of all subjects in the mITT (modified Intent to Treat) set who do not have protocol deviations that may affect key efficacy endpoints, whether or not the deviations are classified as major.

5.0 Study Objectives

The study objectives are as follows.

Safety objective: To assess the safety and tolerability of escalating doses of intravenously administered ganaxolone as determined by adverse events, physical examination, C-SSRS, and change since baseline in:

1) laboratory measures,
2) vital signs,
3) electrocardiogram (ECG), and
4) Stanford Sleepiness Scale (SSS).

Efficacy objective: To explore the efficacy of escalating doses of intravenously administered ganaxolone in the treatment of postpartum depression (PPD) by:

1) Hamilton Depression Rating Scale 17-item version (HAMD17),
2) Edinburgh Postnatal Depression Scale (EPDS),
3) Spielberger State-Trait Anxiety Inventory 6-item version (STAI6) and
4) Clinical Global Impression-Improvement (CGI-I) scale.

Pharmacokinetic objective: To collect samples of blood for pharmacokinetic analysis after administration of intravenous (IV) ganaxolone. Pharmacokinetic analyses will be not be performed by PRA; as such, PK analysis details are beyond the scope of this SAP.

6.0 Study Design

6.1 General Description

This is a Phase 2A, double-blind, placebo-controlled, multiple-dose escalation study consisting of up to 6 cohorts (Cohort 1 to 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, with Cohorts 4 and 5 optional. Approximately 10-30 subjects will be randomized into each cohort. Randomized subjects will receive ganaxolone or matching placebo in a 1:1 ratio. The study will be conducted in the United States at approximately 15 investigative sites.

Figure 1 Study Design.

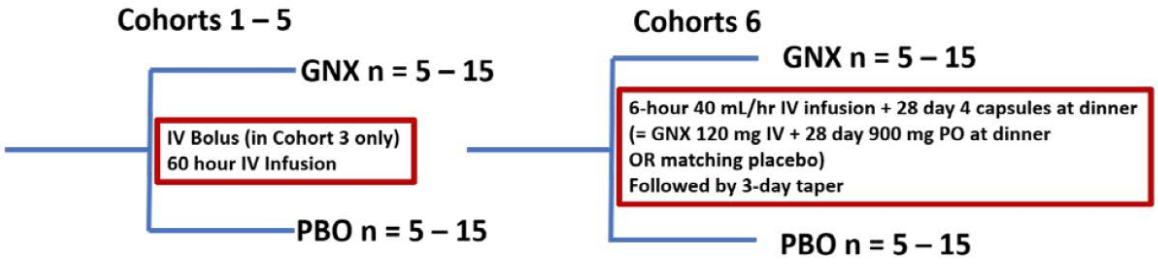

Table 1. Schedule of Assessments – Cohorts 1-5

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	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	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		

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**
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

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.

Cohorts 1-5 will involve IV infusions only, henceforth referred to as IV only cohorts, while Cohort 6 will involve both IV and oral study drug, henceforth referred to as the IV-to-oral cohort.

The IV only cohorts will include a screening visit followed by a screening period up to 2 weeks, a baseline/randomization visit followed by an inpatient 4-day treatment phase during which the subjects will receive a 60-hour infusion of ganaxolone or placebo (with or without bolus). The subject will be discharged from the unit on the morning of Day 4. There will be a follow-up period of 30 days after discharge during which the subject will have safety visits at week 1 (Day 11) and week 4 (Day 34). An unblinded interim safety and efficacy analysis will be conducted by the DRC after each cohort for the purpose of dose selection for the next cohort. The total duration of study participation will be up to 7 weeks.

The IV-to-oral cohort (Cohort 6) will include a screening visit followed by a screening period up to 2 weeks, a baseline/randomization visit followed by an inpatient 1-day treatment phase during which the subjects will receive a 6-hour infusion of ganaxolone or placebo from approximately 9 am to 3 pm followed by the start of oral dosing at approximately 7 pm. The subjects will be admitted 1 day prior to Day 1 (infusion day) and discharged from the unit in the morning of Day 2. Oral dosing is continued as outpatient on Days 2-28. There will be 3 safety follow-up visits after the last dose, at Weeks 1, 4, and 6. The total duration of study participation will be up to 12 weeks.

The dosing regimen for each cohort 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 4-5: 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: 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).

6.2 Sample Size Considerations

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 and on DRC recommendations. 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.

6.3 Randomization

Approximately 200 women 18–45 years of age will be screened, and approximately 10-30 of those with PPD will be randomized within cohorts on Day 1 to receive ganaxolone or placebo in a 1:1 ratio with 1 block

of 4 for each cohort, while the rest of the blocks are of size 2. Treatment assignment will be determined by a randomization schedule prepared by PAREXEL. Randomization will not be stratified. Treatment assignments will be obtained by the investigator (or designee) via an Interactive Voice and/or Web Response System (IxRS). Subject numbers will be assigned sequentially as subjects consent to participate in the study. After being randomized a subject will be replaced only if she discontinues prior to receiving investigational product (IP). The replacement subject will receive the same IP assignment as the replaced subject.

6.4 Blinding

The unblinded pharmacist, unblinded medical monitor, independent reporting statistician/programmers, as well as the DRC are provided the treatment information prior to unblinding in order to ensure the optimal conduct of the study. In addition, any data transferred into PRA are processed by an unblinded database developer in order to ensure any potentially unblinding information is masked to the study team. All other study personnel remain blinded to treatment assignment until unblinding.

The unblinded statistician and programming team are external to PRA and have limited communication with the blinded statistician and programmers during the conduct of this study.

7.0 Study Variables and Covariates

7.1 Efficacy

7.1.1 HAMD17

The Hamilton Depression Rating Scale (HAMD) is a commonly-used semi-structured clinician-rated instrument which assesses the range of symptoms that are most frequently observed in subjects with major depression. All items are scored on an ordinal scale between 0 and 4 (8 items) or 0 and 2 (9 items) of increasing severity. A total score is derived by summing over all individual items. Improvement is indicated by negative change scores and this will be footnoted in the TFLs. The 17-item version of this scale (HAMD17) will be used in this trial and will be assessed at each in-person study visit . The Day 1 assessment before IP infusion will be the Baseline observation.

7.1.2 HAMD6

Some items on the HAMD scale (such as weight) are not expected to have meaningful changes over the first 72 hours. The 6-item version of the HAMD, known as HAMD6, will be 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. The HAMD6 is considered to be responsive to more immediate changes in depression symptoms. Improvement is indicated by negative change scores and this will be footnoted in the TFLs.

7.1.3 Edinburgh Postnatal Depression Scale (EPDS)

The EPDS is a 10-question self-rated instrument for assessment of symptoms of PPD such as worry, sleep, mood and enjoyment, which are rated on a 4-point scale (0 to 3) of increasing severity. The EPDS total score is the sum of the scores of these 10 questions. Improvement is indicated by negative change scores and this will be footnoted in the TFLs.

Two questions assessing obsessive thoughts were 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 EPDS score. These 2 questions are rated on a 5-point scale (0 to 4) of increasing severity.

The responses will be assessed at Screening, Day 1, +60h, Day 11, and Day 34 for the IV only cohorts and at each in-person visit for the IV to oral cohort. The Day 1 assessment before IP infusion will be the Baseline observation.

7.1.4 Spielberger Trait-State Anxiety Inventory, 6 item version

The Spielberger Trait-State Anxiety Inventory, six item version (STAI6), is a short questionnaire evaluating anxiety state. The STAI6 has 6 questions: 1) “I feel calm”, 2) “I am tense”, 3) “I feel upset”, 4) “I am relaxed”, 5) “I feel content”, and 6) “I am worried". Each of these questions are rated as a) “not at all” b) “somewhat”, c) “moderately”, and d) “very much.” For questions 2, 3, and 6, the scoring is a=1, b=2, c=3, and d=4. For the other 3 questions, the scoring is a=4, b=3, c=2, and d=1. The STAI6 score is the result of first totaling the 6 individual item scores, and then prorating it by a multiplication factor of 20/6 to acquire a range of 20 to 80, inclusive (Marteau 1992). Improvement is indicated by negative change scores and this will be footnoted in the TFLs.

The responses will be assessed at each post-baseline in-person visit except Day 0 (admission). The Day 1 assessment before IP infusion will be the Baseline observation.

7.1.5 Clinical Global Impression-Improvement (CGI-I)

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.

CGI-I responses will be assessed at each post-baseline in-person visit.

7.2 Safety

7.2.1 Adverse Events (AE)

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. Data on AEs will be collected at each visit from the time the informed consent is signed until the end of the follow-up period. This includes AEs occurring during the screening phase of the study, regardless of whether or not investigational product has been administered. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 20.0. Rules for partial dates are provided in Appendix 2.

7.2.2 Laboratory Measures

Laboratory measures will be assessed at Screening, Day 0, +48h, and Day 11 for the IV only cohorts and at Screening and Days 0, 8, 15, 29, and 57 for the IV to oral cohort. Urine pregnancy tests and drug screens will be conducted at Screening, Day 0, +72h, and Days 11 and 34 for the IV only cohorts and at Screening and at Days 0, 8, 15, 22, 29, 36, 57, and 71. The Day 0 assessment will be the Baseline observation. Neurosteroid levels and PK data will be analyzed separately by other third-party vendors and thus will not be described in this SAP. Per protocol, the following assessments will be done.

- Chemistry: 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), β-HCG (Human Chorionic Gonadotropin)

- 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

- Urinalysis: Leukocytes, nitrites, protein, blood, specific gravity, glucose, ketones

- Urine Drug Screen: Cannabis, oxycodone, methadone, buprenorphine, cocaine, benzodiazepines, barbiturates, alcohol (ethanol) and phencyclidine

  Urine pregnancy results will only be provided in a data listing.

7.2.3 Vital Signs, Height, and Weight

Vital signs will be assessed at each in-person study visit . The following measurements will be taken:.

a. Systolic blood pressure (mmHg)
b. Diastolic blood pressure (mmHg)
c. Pulse rate (beats/min)
d. Oral body temperature (degrees Celsius)
e. Respiratory rate (breaths/min)
f. Pulse Oximetry (%)
g. Height (cm) (collected only at Screening)
h. Weight (kg) (collected only at Screening and Days 0, 11, and 34 for the IV only cohorts and at Screening and Days 15, 29, 36, 57, and 71 for the IV to oral cohort)
a. Body Mass Index (kg/m^2)

The Day 1 assessment before IP infusion will be the Baseline observation for vital signs. For weight, the Day 0 assessment will be the Baseline observation.

7.2.4 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a unique, simple, and short method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. 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.

C-SSRS will be assessed at each in-person study visit. The Day 1 assessment before IP infusion will be the Baseline observation.

7.2.5 Stanford Sleepiness Scale (SSS)

Stanford Sleepiness Scale (SSS) is a self-rated scale (1 to 8 of increasing sleepiness) 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.

The responses will be assessed at Day 1 before infusion, +8h, +32h, +56h, and +72h for the IV only cohorts and at Day 1 before infusion, +6h and at Days 2, 8, 15, 22, 29, 36, 57, and 71 for the IV to oral cohort. The Day 1 assessment before IP infusion will be the Baseline observation.

7.2.6 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be conducted at Screening, Day 0, Day 1 before infusion, +12h, +24h, +48h, and +72h for the IV only cohorts and at Screening, +6h, and at Days 0, 2, 8, 15, 22, 29, and 36 for the IV to oral cohort. The Day 1 assessment before IP infusion will be the Baseline observation for the IV only cohorts. For the IV to oral cohort, the Day 0 assessment will be the Baseline observation. RR, PR, QRS, QTcF and QTcB will be collected. Continuous measures will be imported from an external vendor database. The data will undergo vendor specific edit checks. Reconciliations with EDC will be performed upon import of data to PRA.

7.2.7 Physical Examination

A complete physical examination will be performed at Screening and +72h for the IV only cohorts and at Screening and at Days 2, 15, and 29 for the IV to oral cohort.

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

- Autoimmune
- Cardiovascular
- Dermatological
- Ears, Nose, Throat
- Endocrine/Metabolic
- Gastrointestinal
- Genito-urinary
- Musculoskeletal
- Respiratory
- Central Nervous System

8.0 Definitions

8.1 Treatment/Subject Grouping Definition

Throughout this SAP treatment refers to active or placebo. Dose refers to the dose level of the active treatment.

Label	Definition
Study Drug	Ganaxolone
Treatment	Ganaxolone or Placebo
Dose Levels	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/r 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: 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.

8.2 Other Definitions

+72h

72 hours after start of infusion (0hr) based on visit window. If a subject is discontinued from the study during the inpatient treatment phase (Day 1 through Day 4), all assessments scheduled at +72h will be collected at the time of study exit, but the assessments will be allocated to analysis visits based on visit windows detailed in Section 8.4.

Age

The following SAS® code will be used to calculate subject age (years):

Age = floor ([intck{'month', birth date, screen date} - {day(informed consent date) < day(birth date)}] / 12), where intck is a SAS® function counting integer days.

Baseline

Baseline is defined as the last non-missing assessment prior to the first dose of study drug. The last observation can be an unscheduled/repeated measurement. In most cases, the time point just before "start of infusion" or "0hr" will be treated as the baseline, but if this observation is missing in a given period then the screening value may be used.

Change from Baseline

Change from baseline (CFB) will be calculated as (post-baseline – baseline).

Discontinuation of study

A subject will be considered discontinued from the study when a Study Exit CRF page is completed indicating primary reason for discontinuation.

Protocol deviation

Potential planned or unplanned protocol deviations noted during clinical monitoring will be documented by category (i.e., inclusion criteria, exclusion criteria, study drug, safety assessment, efficacy assessment, visit window, informed consent, prohibited medication, and other) and by whether or not the deviation excludes

the subject from the per protocol analysis set. All deviations will be reviewed, categorized, and finalized prior to database lock.

Relationship to study treatment
AEs related to study treatment will be defined as those entered as Related or Not Related. If relationship is missing, then it will be considered as related to study treatment.

Study day
Study day is defined relative to the date of the first dose of study drug. For assessments that occur after this visit date, study day is calculated as (assessment date – study drug first dose date + 1). For assessments that occur prior to study drug first dose date, study day will be calculated as (assessment date – study drug first dose date); there is no Study Day 0.

Study time
Study time (in minutes) is defined relative to the time of the first dose of study drug (0 hour on the morning of Day 1).

8.3 Imputation

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 in summaries and analyses unless otherwise noted.

8.4 Analysis Time Point/Visit Windows

For data summarized on a per time point or per visit basis, the windows used for analyses are defined below unless stated otherwise.

For the IV only cohorts (cohorts 1-5), the following analysis time points and visit windows will be used.

Protocol Visit	Window Description (Target Day/Time Point)	Protocol Window (with respect to Visit Day as defined in the protocol)	Analysis Window (with respect to Study Day and Study Time in minutes as defined in this SAP)
Screening	Screening	Day -14 to -1	Study Day < -1
Day 0	Day 0 (Admission)	Day 0	Study Day = -1
Day +1	Day 1 (Pre-Infusion)	N/A	Study Day = 1 and Study Time < 0
Day +1	Day 1 (+4h)	N/A	0 <= Study Time < 360
Day +1	Day 1 (+8h)	N/A	360 <= Study Time < 600
Day +1	Day 1 (+12h)	N/A	600 <= Study Time < 900
Day +1	Day 1 (+18h)	N/A	900 <= Study Time < 1260
Day +2	Day 2 (+24h)	N/A	1260 <= Study Time < 1680
Day +2	Day 2 (+32h)	N/A	1680 <= Study Time < 2160
Day +2	Day 2 (+40h)	N/A	2160 min <= Study Time < 2640 min
Day +3	Day 3 (+48h)	N/A	2640 min <= Study Time < 3120 min
Day +3	Day 3 (+56h)	N/A	3120 min <= Study Time < 3480 min
Day +3	Day 3 (+60h)	N/A	3480 min <= Study Time < 3960 min
Day +4	Day 4 (+72h)	N/A	3960 min <= Study Time < 2 days after 72 hr timepoint

Protocol Visit	Window Description (Target Day/Time Point)	Protocol Window (with respect to Visit Day as defined in the protocol)	Analysis Window (with respect to Study Day and Study Time in minutes as defined in this SAP)
Day 11	Day 11	Day 8 to 14	5 <= Study Day < 23
Day 34	Day 34	Day 29 to Day 39	23 ≤ Study Day < 45

For the IV to oral cohort (cohort 6), the following analysis time points and visit windows will be used.

Protocol Visit	Window Description (Target Day/Time Point)	Protocol Window (with respect to Visit Day as defined in the protocol)	Analysis Window (with respect to Study Day and Study Time in minutes as defined in this SAP)
Screening	Screening	Day -14 to -1	Study Day < -1
Day 0	Day 0 (Admission)	Day 0	Study Day = -1
Day +1	Day 1 (Pre-Infusion)	N/A	Study Day = 1 and Study Time < 0
Day +1	Day 1 (Post-Infusion)	N/A	Study Day = 1 and Study Time >= 0
Day 2	Day 2 (Discharge)	N/A	Study Day = 2
Day 4	Day 4 (HAMD Call)	Day 3 to 5	3 <= Study Day <= 5 for HAMD only
Day 8	Day 8	Day 6 to 10	6 <= Study Day <= 9 for HAMD, 3 <= Study Day <= 11 otherwise
Day 11	Day 11 (HAMD Call)	Day 10 to 12	10 <= Study Day <= 12 for HAMD only
Day 15	Day 15	Day 12 to 18	13 <= Study Day <=18 for HAMD, 12 <= Study Day <= 18 otherwise
Day 22	Day 22	Day 19 to 25	19 <= Study Day <= 25
Day 29	Day 29	Day 26 to 32	26 <= Study Day <= 32
Day 36	Day 36	Day 33 to 39	33 <= Study Day <= 46
Day 57	Day 57	Day 54 to 60	47 <= Study Day <= 64
Day 71	Day 71	Day 68 to 74	65 <= Study Day <= 77

The analysis windows are aligned with, but wider than, those specified by the schedule of visits and procedures in the protocol in order to include in analyses of all study data (including unscheduled visit data) that fall outside of protocol visit windows. If multiple data points are observed within a single analysis window, the latest observation will be used for analysis.

9.0 Analysis Sets

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

The **Randomized Set** will consist of all subjects who were 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 (PP) Set** will consist of all subjects in the mITT set who do not have protocol deviations that may affect key efficacy endpoints.

The **Infusion Completer Set** will consist of all subjects in the IV only cohorts (cohorts 1-5) who completed the 60-hour infusion and all subjects in the IV to oral cohort (cohort 6) who completed the initial infusion.

The **Completer Set** will consist of all subjects in the IV only cohorts who completed the 60-hour infusion and attended all outpatient visits, and all subjects in the IV to oral cohort who completed the initial infusion and oral IP dosing period with at least 80% oral dosing compliance and attended all outpatient visits.

Subjects in the Safety Set will be analyzed according to the actual treatment received. Subjects in the Randomized, mITT, and both completer sets will be analyzed according to assigned treatment regardless of actual treatment received.

10.0 Analyses

10.1 Data Review Committee (DRC)

Interim unblinded analyses of safety and efficacy data will be conducted by a Data Review Committee (DRC) during the study, separate from the blinded study team. The DRC is composed of the Marinus Chief Medical Officer and at least two 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 and analysis of clinical trial data. Additional expert members will include an independent contractor statistician (DRC statistician) and a pharmacokineticist (DRC pharmacokineticist).

It is the DRC's responsibility to weigh the risks and benefits of ganaxolone after each interim analysis and make a recommendation on whether the study or cohort should be continued or stopped. The DRC will also provide a recommendation for the next dosing regimen 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.

For the purpose of the DRC meetings, a snapshot of the clinical trial database will be delivered to the DRC statistician who will generate necessary tables, figures and listings (TFLs) needed for the DRC data review. These analyses will be specified in a separate document agreed upon between the DRC and Marinus. The randomization list will be delivered directly to the DRC statistician, who will perform unblinding. The Marinus and PRA study teams will remain blinded until after each cohort database lock.

Pharmacokinetic data will be transferred to the DRC pharmacokineticist directly from the pharmacokinetic analysis vendor (QPS Inc) using a password protected file.

The TFLs generated for the DRC meetings are separate from the TFLs prepared following each database lock, as described below.

10.2 Analyses After Cohorts 1-3

An unblinded analysis of efficacy and safety data for Cohorts 1-3 will be conducted after the last patient in Cohort 3 has completed her final visit (or withdrawn from the study), all clinical data have been entered into the data capture system, AE and concomitant medication data have been coded, quality control checks have been completed, all data queries have been resolved, protocol deviations and the per protocol analysis set have been identified, and the database has been locked. TFLs for subject disposition, demographics and baseline characteristics, efficacy, and AEs will be produced external to PRA.

The continuing trial subsequent to Cohort 3 will again be conducted in a double-blind fashion.

10.3 Final Analysis

The unblinded final analysis will occur when all subjects in the final cohort have completed their final visit (or withdrawn from the study), all clinical data have been entered into the data capture system, AE and concomitant medication data have been coded, quality control checks have been completed, all data queries have been resolved, protocol deviations and the per protocol analysis set have been identified, and the database has been locked. However, Sponsor may decide to stop the study, or make all or a portion of the data public, at any time during any cohort.

If Sponsor chooses to unblind and/or make public all or any portion of the data before database lock, the following processes will be in place:

- A cutoff date or study visit will be established, referred to as the “cutoff time point.”
- A database freeze procedure will be performed in a blinded manner for data collected up to and including the cutoff time point. Documentation of the database freeze procedure will include a detailed description of the specific data that were cleaned prior to the freeze, the timing of temporarily eliminating site access to the database for additional data entry during the freeze, the duration of the freeze, the specific portions of the database that will be unfrozen so that data entry can continue, and procedures for validating that the data up to and including the cutoff time point were not changed post freeze.
- Key personnel required to produce SDTMs, ADaMs, and TFLs will be unblinded at the subject level after database freeze. This will include programmers and statisticians but not other members of the data management team, nor any other members of the clinical team, nor any other representatives of Sponsor. Specific personnel who are unblinded at this stage will be documented. Data listings produced for quality control purposes will not display unblinded treatment assignments from cohorts for which hard lock has not yet occurred.
- Any data summaries or other trial-level data presentations containing unblinded data will consist only of data from the frozen portion of the database until the complete database has been locked.
- Any study personnel with exposure to unfrozen, unblinded data prior to database lock will not be involved in decisions that result in changes to the data or the analysis plan until the complete database has been locked and the study has been formally unblinded.
- Three sets of summaries and analyses will be produced: (1) a topline set that includes data only up to and including the cutoff time point to be delivered before database lock and formal unblinding, (2) the same topline set rerun and revalidated after database lock and formal

unblinding, and (3) a complete set that includes all data, to be delivered after database lock and formal unblinding.

- Analyses of primary and secondary endpoints will consist only of data up to and including the cutoff time point. Any analysis that includes data that were not part of the frozen portion of the database will be exploratory.

11.0 Data Review

11.1 Data Handling and Transfer

PRA will provide data handling and transfer in accordance with Data Management Plan and Data Transfer Plan both dated 12Nov2018.

11.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFL) provides additional data screening. Presumed data issues will be output into SAS logs identified by the word “Problem” and extracted from the logs by a SAS macro and sent to Data Management.

Reviews of a pre-lock TFL run (if included in the study contract) allow for further data screening prior to lock. The PRA statistician and the sponsor must approve database lock.

12.0 Statistical Methods

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.

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), first and third quartiles (Q1 and Q3), minimum (min) value, median, and maximum (max) value. The minimum and maximum values will be displayed to the same level of precision as the raw data, the median and mean to a further decimal place and the SD to two additional decimal places – up to 4 decimal places total.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of subjects exposed within a treatment. Percentages will be rounded to one decimal place.

All analyses will use SAS version 9.4 or higher. Tables will present data summarized by treatment group within cohort. For each summary table, corresponding supportive listing(s) will be provided.

12.1 Subject Disposition

The summary of subject disposition will include number and percentage of subjects in each analysis set, subject status at the end of the trial (completed or discontinued), and reason for discontinuation.

12.2 Important Protocol Deviations

Per PRA processes, protocol deviations will be entered into our Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the deviation data from CTMS

and the resulting set of evaluable subjects throughout the study, adjusting the deviation criteria as seems appropriate. The Per Protocol set must be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

Protocol deviations (see definition in Section 8) for subjects in the Safety Set will be summarized by category. Examples of categories that may be used are inclusion criteria, exclusion criteria, study drug, safety assessment, lab/endpoint data, visit window, informed consent, prohibited medication, overdose/misuse, and other.

12.3 Treatments

12.3.1 Extent of Study Drug Exposure

12.3.1.1 IV Only Cohorts

For each IV only cohort, duration of IV exposure (hours), total dose (mg), and mean daily dose (mg) will be summarized for the Safety set, calculated as follows:

Duration of Exposure = $\sum t_v + \sum t_b - \sum t_i$ where:

t_v = all IV/infusion administration time intervals, calculated as end date/time – start date/time (hrs)

t_b = all bolus administration time intervals, calculated as end date/time – start date/time (hrs)

t_i = all IV/infusion interruption time intervals, calculated as stop time – start time (hrs). Note: $\sum t_i$ = Total Duration of Interruptions

Note: Since interruption start/end times but not start/end dates are collected, if end time > start time, it will be assumed that start date = end date; otherwise, it will be assumed that end date = start date + 1.

Total Dose = $\sum(t_v r_v c) + \sum v_b c - \sum(t_i r_i c)$ where:

t_v *and* t_i are as defined above (hr)

r_v = infusion rate (mL/h)

r_i = infusion rate at start of interruption (mL/h) Note: since neither infusion rate nor date at start of interruption is collected, it will be assumed that r_i is the same as infusion rate at end of interruption (which is collected), unless otherwise instructed by Sponsor.

c = concentration (mg/mL) Note: Concentration for subjects treated with ganaxolone is cohort-dependent. Concentration for placebo subjects is 0.

v_b = volume of bolus injected (mL)

Mean Daily Dose = $\frac{\text{Total Dose}}{\text{Overall Days Exposed}}$ where:

Overall Days Exposed = last end date of last IV/infusion or bolus administration – first start date of first IV/infusion or bolus administration + 1.

Details of infusion interruptions and early discontinuations will be listed.

12.3.1.2 IV to Oral Cohort

For the IV to oral cohort, duration of IV exposure (hours), duration of oral exposure (days), total duration of exposure (days), IV dose (mg), oral dose (mg), total dose (mg), mean daily IV dose (mg), mean daily oral dose (mg), and mean daily total dose (mg) will be summarized for the Safety set, calculated as follows:

Duration of IV Exposure = $\sum t_v - \sum t_i$ where

t_v = all IV/infusion administration time intervals, calculated as end date/time – start date/time (hrs)

t_i = all IV/infusion interruption time intervals, calculated as stop date/time – start date/time (hrs). Note: $\sum t_i$ = Total Duration of Interruptions

Duration of Oral Exposure = date of last oral exposure – date of first oral exposure + 1

Total Duration of Exposure = date of last exposure – date of first exposure + 1

IV Dose = $\sum(t_v r_v c) - \sum(t_i r_i c)$ where:

t_v *and* t_i are as defined above (hr)

r_v = infusion rate (mL/h)

r_i = infusion rate at start of interruption

c = concentration (mg/mL) Note: Concentration for subjects treated with ganaxolone is cohort-dependent. Concentration for placebo subjects is 0.

Oral Dose = $\sum k_v c$ where:

k_v = number of capsules taken during the vth interval of oral dosing, where each interval is defined by a fixed number of capsules taken per day

c = concentration (mg) Note: Concentration for placebo subjects is 0.

Total Dose = IV dose + oral dose

Mean Daily IV Dose = $\frac{\text{IV Dose}}{\text{Days Exposed to IV Dose}}$ where:

Days Exposed to IV Dose = last end date of last IV/infusion– first start date of first IV/infusion + 1.

Mean Daily Oral Dose = $\frac{\text{Oral Dose}}{\text{Days Exposed to Oral Dose}}$ where:

Days Exposed to Oral Dose = date of last oral exposure – date of first oral exposure + 1.

Mean Daily Total Dose = $\frac{\text{Total Dose}}{\text{Total Days Exposed}}$ where:

Total Days Exposed = date of last exposure – date of first exposure + 1.

Details of infusion interruptions and discontinuations will be listed.

Oral compliance will be summarized and will be calculated as:

$$100 \text{ x } \left[\frac{\text{Total Actual Oral Dose}}{\text{Total Expected Oral Dose}}\right]$$

where Actual Oral Dose will be based on returned capsule count.

12.3.2 Concomitant Medications

A concomitant medication is defined as any medication taken between the screening visit and the end of the follow-up period (i.e., the end date is on or after the screening visit date, or the subject is still taking the medication at the end of the follow-up period) regardless of the start date of the medication. Medications recorded with insufficient exposure dates to determine whether or not they were concomitant will be considered concomitant.

Concomitant medications will be categorized by preferred term according to WHO (World Health Organization) Drug Dictionary (Version 01DEC2017 Drug Dictionary Enhanced (DDE)) and will be summarized for the Safety Set. The number and percentage of subjects using each medication will be displayed for each preferred term.

12.4 Demographic and Baseline Characteristics

12.4.1 Demographics

The following demographic and other baseline characteristics will be summarized for the Safety Set:

- Sex (female)
- Age (years)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight (kg)
- Height (cm)
- Body mass index (kg/m^2)

12.4.2 Medical History

Medical history will be tabulated for the Safety Set by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA Version 20.0.

12.4.3 Prior Medications

Prior medications are defined as medications with an end date prior to the screening visit date. If a partial date allows a medication to be considered a prior medication, it will be categorized as such.

Prior medications will be categorized by preferred term according to WHO Drug Dictionary (Version 01DEC2017 DDE) and will be summarized for the Safety Set. The number and percentage of subjects using each medication will be displayed for each preferred term.

12.4.4 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 conducted only at the screening visit. MINI data will not be summarized but will be presented in a data listing.

12.4.5 SAFER Interview

Staff psychiatrists or psychologist at the Massachusetts General Hospital Clinical Trials Network and Institute 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 patients

who are deemed eligible for randomization to confirm validity of the diagnosis of PPD and eligibility for the study from depression perspective.

Time of SAFER interview and whether a subject is eligible based on inclusion criteria will be listed.

12.4.6 Clinical Global Impression – Severity Scale

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.

CGI-S responses will be assessed at Screening and Day 1 before infusion (Baseline) and will be summarized.

12.5 Efficacy Analyses

Statistical analysis of efficacy endpoints will primarily be done using the mITT set and will be done only to aid in interpretation as the trial was not powered for inferential hypothesis testing. As such, there will be no adjustments for inflation of type 1 error due to multiplicity.

For efficacy endpoints expressed as continuous variables, summary tables will show continuous summary statistics for each time point of data collection (visit) as well as least squares (LS) means with standard errors (SEs) and associated p-values from mixed model repeated measures (MMRM) analysis. Summary statistics by time point will also be displayed graphically using bar and/or line charts. MMRM models will include fixed effects for treatment, visit, and the treatment-by-visit interaction, and the baseline observation will be included as a covariate. Repeated measurements are made on each subject. Residuals will be evaluated for substantial departure from normality and independent and constant variance. Methods such as data transformation, detecting and assessing the influence of outliers, and alternative analytical approaches (e.g., non-parametric) may be used to address assumption deviations. An unstructured covariance will be the default covariance structure but other structures (e.g., compound symmetry) may be used to evaluate sensitivity to the choice of structure or, if necessary, to achieve convergence. MMRM assumes missing observations are missing at random (MAR); i.e., missingness depends only on variables other than the outcome that are available in the database. Because the MAR assumption is not testable, and because it seems possible that subjects with poorer outcome may be more likely to miss trial assessments, a sensitivity analysis may be done in which all missing data will be imputed. Conservatively, multiple imputation with a pattern-mixture model will be used; specifically, for all subjects with missing observations regardless of treatment assignment, imputation will be based only on subjects randomized to placebo. The imputation method will be *fully conditional specification (FCS) regression with 25 imputations*. Variables in the imputer's model will be observed values at each time point included in the MMRM analysis, including baseline.

For efficacy endpoints expressed as categorical (including binary) variables, summary tables will show frequencies and percentages of subjects in each category as well as adjusted event rates with SEs and associated p-values using general estimating equations (GEE). Summary statistics by time point will also be displayed graphically using bar charts. GEE models will include main effects for treatment and visit and an interaction term for treatment-by-visit. Baseline will be included as a covariate where applicable. Unstructured covariance will be specified but alternative structures (e.g., CS) or alternative statistical methods (e.g., chi square tests of association) may be used if GEE convergence cannot be achieved. GEE assumes missing observations are missing completely at random (MCAR); i.e., missingness is independent of all other information whether it was collected or not. A sensitivity analysis based on multiple imputation, as described above, may be done in which FCS logistic regression would be the imputation method.

12.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be HAMD17 total score change from baseline to 60 hours post-infusion (on Day 3) for the IV only cohorts and to Day 29 for the IV to Oral cohort. 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.

12.5.2 Secondary Efficacy 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 rating

12.5.3 Exploratory Efficacy Endpoints and Analyses

[redacted]

[redacted]

12.6 Safety Analyses

Unless otherwise stated in the subsections below, the following safety variables will presented in listings and analyzed in summary tables containing summary statistics and change from baseline by treatment arms for each study time point. All safety analyses will be based on the Safety Set.

1) Laboratory measures, including urine drug screen
2) Vital signs
3) Electrocardiogram (ECG)
4) Stanford Sleepiness Scale (SSS).

12.6.1 Adverse Events

AEs reported from screening through EOS will be coded according to MedDRA® (Medical Dictionary for Regulatory Activities) version 20.0 or greater. Each reported AE will be mapped to a Preferred Term (PT) and a System Organ Class (SOC).

A treatment-emergent AE (TEAE) will be defined as an AE that began or worsened after the first dose of IP and no later than 30 days after the last dose of IP. AEs with insufficient date or time information to determine whether or not they were treatment-emergent will be considered treatment-emergent.

All TEAEs will be listed. In addition, separate listings will be done for non-treatment-emergent AEs and serious AEs (SAEs), treatment-emergent SAEs, and TEAEs that resulted in death, IP discontinuation, IP interruption, or dose reduction. Listings will include reported term, PT, and SOC; start and stop date; whether or not the AE was serious; severity; whether or not the AE was related to IP; action taken; and outcome.

Incidence and number of TEAEs will be summarized by SOC and PTs within SOCs. Summaries will include assessments of severity and relationship to IP. Missing severity will be considered severe and missing relationship will be considered related. Only the most related TEAE per subject for a given PT will be counted in summaries by relationship; similarly, only the most severe TEAE will be counted in summaries by severity. Separate summaries will be done for TEAEs related to IP and TEAEs resulting in IP discontinuation or interruption, or dose reduction. Summaries will be done separately for (a) all TEAEs and (b) treatment-emergent SAEs only.

12.6.2 Laboratory Data

In addition to change from baseline summary tables for quantitative lab parameters, out of range lab observations will be determined using reference ranges provided by MedPace Laboratory and will be flagged in data listings.

Over the course of the study, there may be some lab tests performed that are not mentioned in the protocol. These tests will not be summarized but will be included in the listings.

Neurosteroid levels will be not be performed by PRA, as such, neurosteroid levels analysis details are beyond the scope of this statistical analysis plan.

12.6.3 Vital Signs

Vital signs will be analyzed as continuous variables. In addition to change from baseline summary tables, potentially clinically significant (PCS) observations will be flagged in data listings based on the criteria given in Table 3.

TABLE 3. VITAL SIGNS PCS CRITERIA

Vital Sign	Unit	Low PCS Criteria	High PCS Criteria
Heart rate	bpm	≤50 and decrease of ≥15 from baseline	≥120 and increase of ≥15 from baseline
Systolic blood Pressure	mmHg	≤90 and decrease of ≥20 from baseline	≥180 and increase of ≥20 from baseline
Diastolic blood Pressure	mmHg	≤50 and decrease of ≥15 from baseline	≥105 and increase of ≥15 from baseline
Respiratory rate	Breaths/minute	≤8 and decrease of ≥4 from baseline	≥30 and increase of ≥10 from baseline
Body Temperature	Degree Celsius	≤36 and decrease of ≥1 from baseline	≥38.3 and increase of ≥1 from baseline
Body Weight	%	Decrease of ≥7 from baseline	Increase of ≥7 from baseline
Oximetry	%	≤90%	N/AA

12.6.4 Physical Examinations, 12-Lead ECGs, and Other Observations Related to Safety

12.6.4.1 Physical Examination

Physical examination results will not be summarized but will be provided in a listing.

12.6.4.2 12-Lead ECG

12-lead ECG parameters will be analyzed and transferred externally to PRA. These parameters will be summarized as continuous variables. In addition to summary tables PCS ECG observations will be flagged in data listings based on the criteria given in Table 4.

TABLE 4. ECG PCS CRITERIA

ECG Parameter	Unit	Low PCS Criteria	High PCS Criteria
Heart rate	bpm	≤50 and decrease of ≥15 from baseline	≥120 and increase of ≥15 from baseline
PR Interval	ms	<120 and baseline value ≥120	>210 and baseline value ≤200
QRS Complex	ms	None	>110 and baseline value ≤110
QTcF	ms	None	Prolongation >30 from baseline

12.6.4.3 Pregnancy

All pregnancy results will be listed.

12.6.4.4 Stanford Sleepiness Scale (SSS)

A summary of SSS will show frequency and percentage of subjects at each rating level, and a plot showing mean (SE) SSS at each applicable study time point will be provided.

12.6.4.5 Columbia-Suicide Severity Rating Scale (C-SSRS)

For the 5 suicidal ideation questions (“Wish to be dead,” “Non-specific active suicidal thoughts,” “Active suicidal ideation with any methods (not plan) without intent to act,” “Active suicidal ideation with some intent to act, without specific plan,” “Active suicidal ideation with specific plan and intent”) and the 5 suicidal behavior questions (“Preparatory acts or behavior,” “Aborted attempt,” “Interrupted attempt,” “Suicide attempt,” “Suicide behavior”) of the C-SSRS, the number of subjects who answered “yes” will be tabulated for each applicable study time point. Other data collected on the C-SSRS (e.g., ideation intensity measures) will be provided in data listings only.

13.0 **Validation**

Quality control procedures will be documented separately in the study specific quality control plan.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
CFB	Change from Baseline
CGI-I	Clinical Global Impression - Improvement
CGI-S	Clinical Global Impression – Severity
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTMS	Clinical Trials Management System
DDE	Drug Dictionary Enhanced
DRC	Data Review Committee
ECG	Electrocardiogram
EDPS	Edinburgh Postnatal Depression Scale
FCS	Fully Conditional Specification
GEE	General Estimating Equations
GNX	Ganaxolone
HAMD	Hamilton Depression Rating Scale
HAMD6	Hamilton Depression Rating Scale 6-item version
HAMD17	Hamilton Depression Rating Scale 17-item version
HCG	Human Chorionic Gonadotropin
IP	Investigational Product
IV	Intravenous
IxRS	Interactive Voice and/or Web Response System
MAR	Missing at Random
MCAR	Missing Completely at Random
MedDRA	Medical Dictionary for Regulatory Actvitites
MINI	Mini International Neuropsychiatric Interview
mITT	Modified Intention-to-treat
MMRM	Mixed Model Repeated Measures
PBO	Placebo
PCS	Potentially Clinically Significant

PK	Pharmacokinetic
PP	Per Protocol
PPD	Postpartum Depression
PT	Preferred Term
Q1/Q3	First Quartile/Third Quartile
SAE	Serious Adverse Event
SAFER	State versus trait; Assessability; Face validity; Ecological Validity; and Rule of 3 Ps
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SSS	Stanford Sleepiness Scale
STAI6	Spielberger State-Trait Anxiety Inventory 6-item version
TEAE	Treatment-Emergent AE
TFL	Table, figure and listing
TSH	Thyroid Stimulating Hormone
WHO	World Health Organization

Appendix 2 Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)			
Parameter	**Missing**	**Additional Conditions**	**Imputation**
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing
Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month. Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.			

Appendix 3 Tables, Figures, Listings, and Supportive SAS Output Appendices

List of Post-Text Tables, Figures :		
Output	**Title**	**Analysis Set**
Table 14.1.1	Subject Disposition	Randomized
Table 14.1.2.1	Baseline Characteristics	Safety
Table 14.1.3.X	Medical History by System Organ Class and Preferred Term	Safety
Table 14.1.4.X	Prior Medications by WHO Drug Dictionary Preferred Term	Safety
Table 14.1.5.X	Concomitant Medications by WHO Drug Dictionary Preferred Term	Safety
Table 14.2.1.1.1.1	Observed Values and Changes From Baseline in HAMD17 Total Score	mITT
Table 14.2.1.1.2.1	Observed Values and Changes From Baseline in HAMD17 Bech Subscale (HAMD6)	mITT
Table 14.2.1.1.3.1	Observed Values and Changes From Baseline in HAMD17 Anxiety/Somatization Subscale	mITT
Table 14.2.1.1.4.1	Observed Values and Changes From Baseline in HAMD17 Gibbons Subscale	mITT
Table 14.2.1.2.1.1	HAMD17 Total Score -- Response	mITT
Table 14.2.1.3.1.1	HAMD17 Total Score -- Remission	mITT
Table 14.2.2.1.1.1	Observed Values and Changes From Baseline in EPDS Total Score	mITT
Table 14.2.2.1.2.1	Observed Values and Changes From Baseline in EPDS Anxiety Subscale	
Table 14.2.3.1.1.1	Observed Values and Changes From Baseline in STAI6 Total Score	mITT
Table 14.2.4.1.1	CGI-Improvement	mITT
Table 14.3.1.X	Treatment Exposure (IV/Infusion)	Safety
Table 14.3.1.3	Treatment Exposures	Safety
Table 14.3.2.1	Summary of Treatment-Emergent Adverse Events (TEAEs)	Safety
Table 14.3.2.2.1	Incidence and Number of Treatment-Emergent Adverse Events	Safety
Table 14.3.2.2.2	Incidence and Number of Treatment-Emergent Adverse Events Related to Investigational Product	Safety
Table 14.3.2.2.3	Incidence and Number of Treatment-Emergent Adverse Events Resulting in Investigational Product Discontinuation	Safety
Table 14.3.2.2.4	Incidence and Number of Treatment-Emergent Adverse Events Resulting in Investigational Product Dose Reduction or Interruption	Safety
Table 14.3.2.2.5	Incidence of Treatment-Emergent Adverse Event Preferred Terms in Order of Descending Incidence Among All Subjects	Safety
Table 14.3.2.3.1	Incidence and Number of Treatment-Emergent Serious Adverse Events	Safety

Table 14.3.2.3.2	Incidence and Number of Treatment-Emergent Serious Adverse Events Related to Investigational Product	Safety
Table 14.3.2.3.3	Incidence and Number of Treatment-Emergent Serious Adverse Events Resulting in Investigational Product Discontinuation	Safety
Table 14.3.2.3.4	Incidence and Number of Treatment-Emergent Serious Adverse Events Resulting in Investigational Product Dose Reduction or Interruption	Safety
Table 14.3.2.3.5	Incidence of Treatment-Emergent Serious Adverse Event Preferred Terms in Order of Descending Incidence Among All Subjects	Safety
Table 14.3.3.1.X	Hematology Results by Time Point	Safety
Table 14.3.3.2.X	Biochemistry Results by Time Point	Safety
Table 14.3.3.3.X	Urinalysis Results by Time Point	Safety
Table 14.3.3.4.X	Urine Drug Screen by Time Point	Safety
Table 14.3.4.X	Vital Sign Results by Time Point	Safety
Table 14.3.5.X	Electrocardiogram Results	Safety
Table 14.3.6	Stanford Sleepiness Scale	Safety
Table 14.3.7.X	Columbia-Suicide Severity Rating Scale (C-SSRS) – Suicidal Ideation and Behavior by Time Point	Safety
Figure 14.2.1.1.1.1.1	Mean (SE) HAMD17 Total Score	mITT
Figure 14.2.1.1.1.3.1	Mean (SE) HAMD17 Total Score	mITT
Figure 14.2.1.1.2.1.1	Mean (SE) HAMD17 Bech Subscale (HAMD6)	mITT
Figure 14.2.1.1.2.3.1	Mean (SE) HAMD17 Bech Subscale (HAMD6)	mITT
Figure 14.2.1.1.3.1.1	Mean (SE) HAMD17 Anxiety Subscale	mITT
Figure 14.2.1.1.3.3.1	Mean (SE) HAMD17 Anxiety Subscale	mITT
Figure 14.2.1.1.4.1.1	Mean (SE) HAMD17 Gibbons Subscale	mITT
Figure 14.2.1.1.4.3.1	Mean (SE) HAMD17 Gibbons Subscale	mITT
Figure 14.2.1.1.5.4.1	Mean HAMD17 Individual Items	mITT
Figure 14.2.1.2.1.1	HAMD17 Total Score - Response	mITT
Figure 14.2.1.3.1.1	HAMD17 Total Score - Remission	mITT
Figure 14.2.2.1.1.1.1	Mean (SE) EPDS Total Score	mITT
Figure 14.2.2.1.1.3.1	Mean (SE) EPDS Total Score	mITT
Figure 14.2.2.1.2.1.1	Mean (SE) EPDS Anxiety Subscale	mITT
Figure 14.2.2.1.2.3.1	Mean (SE) EPDS Anxiety Subscale	mITT
Figure 14.2.2.1.3.4.1	Mean EPDS Individual Items	mITT
Figure 14.2.3.1.1.1.1	Mean (SE) STAI6 Total Score	mITT
Figure 14.2.3.1.1.3.1	Mean (SE) STAI6 Total Score	mITT
Figure 14.2.3.1.2.4.1	Mean STAI6 Individual Items	mITT

Figure 14.2.4.1.1.1	CGI-Improvement	mITT
Figure 14.2.4.2.3.1	CGI-Improvement	mITT
Figure 14.3.6	Stanford Sleepiness Scale	Safety

List of End of Text Listings:		
Output	**Title**	**Analysis Set**
Listing 16.1.7.X	Randomization Assignments	Screened
Listing 16.2.1	Subject Disposition	Randomized
Listing 16.2.2.X	Protocol Deviations	Randomized
Listing 16.2.3.X	Subject Analysis Sets	Randomized
Listing 16.2.4.1	Baseline Characteristics	Randomized
Listing 16.2.4.2.X	Medical History	Safety
Listing 16.2.4.3.X	Prior and Concomitant Medications	Safety
Listing 16.2.4.4.X	Mini International Neuropsychiatric Interview (MINI)	Safety
Listing 16.2.4.5.X	SAFER Interview	Safety
Listing 16.2.5.1.X	Study Drug Administration (IV/Infusion)	Safety
Listing 16.2.5.2.X	Study Drug Interruption (IV/Infusion)	Safety
Listing 16.2.5.3.3	Study Drug Administration (Bolus)	Safety
Listing 16.2.6.1	Hamilton Depression Rating Scale 17-Item Version (HAMD17)	Randomized
Listing 16.2.6.2	Edinburgh Postnatal Depression Scale (EPDS)	Randomized
Listing 16.2.6.3	Spielberg Trait-State Anxiety Inventory 6-Item Version (STAI6)	Randomized
Listing 16.2.6.4	Clinical Global Impression – Improvement (CGI-I)	Randomized
Listing 16.2.6.5	Obsessive Thoughts	Randomized
Listing 16.2.7.1	Treatment-Emergent Adverse Events	Safety
Listing 16.2.7.2	Treatment-Emergent Serious Adverse Events	Safety
Listing 16.2.7.3	Treatment Emergent Adverse Events Resulting in IP Discontinuation	Safety
Listing 16.2.7.4	Treatment Emergent Adverse Events Resulting in IP Dose Reduction or Interruption	Safety
Listing 16.2.7.5	Treatment-Emergent Adverse Events Resulting in Death	Safety
Listing 16.2.7.6.1	Non-Treatment-Emergent Adverse Events	Screened
Listing 16.2.7.6.2	Non-Treatment-Emergent Serious Adverse Events	Screened
Listing 16.2.8.1.X	Hematology Results (Quantitative Parameters)	Safety
Listing 16.2.8.2.X	Biochemistry Results (Quantitative Parameters)	Safety

Listing 16.2.8.3.X	Urinalysis Results (Quantitative Parameters)	Safety
Listing 16.2.8.4.X	Clinical Laboratory Results (Semi-Quantitative and Qualitative Parameters)	Safety
Listing 16.2.8.5.X	Urine Pregnancy Test Results	Safety
Listing 16.2.9.X	Vital Signs	Safety
Listing 16.2.10.1.X	Electrocardiogram Results Part 1	Safety
Listing 16.2.10.2.X	Electrocardiogram Results Part 2	Safety
Listing 16.2.11.X	Physical Examinations	Safety
Listing 16.2.12	Stanford Sleepiness Scale	Safety
Listing 16.2.13.X	Columbia-Suicide Severity Rating Scale (C-SSRS)	Safety