MARINUS PHARMACEUTICALS

STATISTICAL ANALYSIS PLAN

Protocol Title: A Phase 2, Double-blind, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of Oral Administration of Ganaxolone in Women with Postpartum Depression

Protocol Version: Amendment 4, Version 5, October 22, 2018
Protocol Number: 1042-PPD-2003

Statistical Analysis
Plan Author: ██████████████ PhD
Version: Version 1.0
Release Date: November 15, 2018

Study Name: Amaryllis
Study Phase: Phase 2
Product: Ganaxolone (CCD 1042:3α-hydroxy-3β-methyl-5α-pregnan-20-one)
Indication: Postpartum Depression

Sponsor: Marinus Pharmaceuticals, Inc.
                        170 N. Radnor Chester Road
                        Suite 250
                        Radnor, PA 19087
                        USA

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

CONFIDENTIALITY STATEMENT

This document contains confidential and proprietary information of Marinus and is disclosed pursuant to confidentiality and non-disclosure obligations. This information should be used solely for the purposes for which it was provided and should not be copied, shared with, or disclosed to any third party without the express written consent of Marinus.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

APPROVALS

_____

_____   _____
████████████ PhD   Date
████████████ PPD
Consultant to Marinus Pharmaceuticals, Inc.

_____

_____   _____
████████████████   Date
Marinus Pharmaceuticals, Inc.

_____   _____
████████████████ MD   Date
████████████████
████████
Marinus Pharmaceuticals, Inc.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

REVISION HISTORY

Version	Date	Author(s)	Summary of Revision(s)
1.0	███████	███████	New document

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

TABLE OF CONTENTS

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
Δ_G	ganaxolone mean change from baseline
Δ_P	placebo mean change from baseline
AE	adverse event
AIC	Akaike's Information Criterion
ANCOVA	analysis of covariance
BMI	body mass index
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CSSRS	Columbia Suicide Severity Rating Scale
DBPC	double-blind placebo-controlled
DRC	Data Review Committee
ECG	electrocardiogram
EOS	end of study
EPDS	Edinburgh Postnatal Depression Scale
FCS	fully conditional specification
GABA	gamma-aminobutyric acid
GEE	generalized estimating equations
H_A	alternative hypothesis
H_o	null hypothesis
HAMD17	Hamilton Depression Rating Scale 17-item version
ICH	International Conference on Harmonisation
IP	investigational product
IV	intravenous
IxRS	Interactive Voice and/or Web Response System
LS	least squares
MAR	missing at random
MCAR	missing completely at random
MedDRA	Medical Dictionary for Regulatory Activities
MINI	Mini Neuropsychiatric Interview
mITT	modified intent-to-treat
MMRM	"mixed model" for repeated measures
MNAR	missing not at random
OL	open label
PK	pharmacokinetic
PPD	postpartum depression
PT	Preferred Term

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

QHS	every night at bedtime
QIC	Quasilikelihood under the Independence model Criterion
SAE	serious adverse event
SAFER	State versus trait; Assessability; Face Validity; Ecological Validity; and Rule of 3 Ps
SAP	Statistical Analysis Plan
SOC	System Organ Class
SSS	Stanford Sleepiness Scale
STAI6	Spielberger State-Trait Anxiety Inventory 6-item version
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TID	3 times daily
WHO-DD	World Health Organization Drug Dictionary

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

PREFACE

The purpose of this statistical analysis plan (SAP) is to outline the planned analyses and reporting to be completed to support the completion of the Clinical Study Report (CSR) for Marinus Protocol 1042-PPD-2003 (Amaryllis). The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.[1] All work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association[2] for statistical practice.

The following documents were also considered in preparation for writing this SAP:

- Clinical Research Protocol 1042-PPD-2003, Amendment 4, Version 5, October 22, 2018
- International Conference on Harmonisation (ICH) E3 Guideline: Structure and Content of Clinical Study Reports[3]
- ICH E6 Guideline on Good Clinical Practice[4]
- ICH E8 General Considerations for Clinical Trials[5]
- ICH E9 Statistical Principles for Clinical Trials[6]
- Statistical Analysis Plans: Principles and Practice[7]

The SAP is a supplement to the study protocol, which should be referred to for additional details on study design, study conduct, and other operational aspects of the study.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

1. BACKGROUND

Postpartum depression (PPD) is a mood disorder that occurs in women following the birth of a child. Rapid changes in the levels of endogenous neurosteroids during pregnancy are thought to be related to the development of PPD in women who are vulnerable to developing this condition. Plasma levels of allopregnanolone, which is a metabolite of progesterone and an endogenous gamma-aminobutyric acid (GABA) receptor modulator, are known to increase throughout pregnancy and then precipitously drop after delivery. Recently published data demonstrated that a continuous infusion of allopregnanolone rapidly alleviates symptoms of depression in women with PPD. The rationale for this trial is to evaluate whether ganaxolone, a synthetic analog of allopregnanolone, may provide benefit to women with PPD.

2. STUDY OBJECTIVES

The study will consist of two parts: an initial open-label (OL) safety part and a double-blind placebo-controlled (DBPC) part.

2.1 Objectives of the OL Safety Part

The safety objective of the OL safety part is to assess the safety and tolerability of ganaxolone in women with PPD as determined by adverse events (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.

The dosing objective of the OL safety part is to develop an optimal dosing regimen for the DBPC part of the trial.

The efficacy objective of the OL safety part is to assess the efficacy of ganaxolone using 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) scales.

The pharmacokinetic (PK) objective of the OL safety part is to collect samples of blood for PK analysis after administration of oral and intravenous (IV) ganaxolone to use in population-PK analyses, the results of which will be reported separately by the Sponsor.

2.2 Objectives of the DBPC Part

The efficacy objective of the DBPC part is to assess the efficacy of ganaxolone vs. placebo using the HAMD17, EPDS, STAI6, and CGI-I scales.

To safety objective of the DBPC part is to assess the safety and tolerability of ganaxolone vs. placebo in women with PPD as determined by AEs and changes from baseline in laboratory measures, vital signs, CSSRS, ECG, SSS, and physical examination.

The PK objective of the DBPC part is to collect samples of blood for PK analysis after administration of oral doses of ganaxolone to use in population-PK analyses, the results of which will be reported separately by the Sponsor.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

3.   STUDY DESIGN

This is a Phase 2, multicenter study in women with PPD and will consist of two dosing parts: an initial OL safety part followed by a DBPC part. Dosing will be completed for the OL safety part before proceeding to the DBPC part. Schedules of assessments are in Appendix A.

3.1   OL Safety Part

Approximately 172 women with PPD, 18 to 48 years of age, will be screened to enroll approximately 88 subjects into one of three groups, enrolled sequentially:

Group 1: OL TID. The first group of approximately 8 subjects will receive ganaxolone 3 times daily, titrated from 225 mg/day to 900 mg/day over 10 days, followed by a taper over 4 days and a 14-day follow-up period.

Group 2: OL QHS. The second group of approximately 20 subjects will receive ganaxolone at bedtime (QHS) titrated to a dose of 675 mg over 4 days which is then maintained until day 10, followed by a taper over 4 days and a 14-day follow-up period.

Group 3: OL QHS 4-week. The third group of approximately 20 subjects will receive ganaxolone at a dose of 675 mg QHS for 28 days, followed by a taper over 4 days and a 3-month follow-up period.

Group 4: OL 1125 mg. The fourth group of approximately 20 subjects will receive ganaxolone capsules 675 mg at dinner time and 675 mg at bedtime (for a total of 1,350 mg per day) on the first 2 days, followed by 26 days of ganaxolone capsules 1,125 mg at dinner time and a taper over 4 days.

Group 5: OL Bolus-Oral. The fifth group of approximately 20 subjects will receive ganaxolone as IV 12 mg bolus over 2 minutes at approximately 4 pm of the first day, followed by ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime for a total of 1,512 mg on Day 1. On Day 2, subjects will receive ganaxolone oral suspension 750 mg at dinner time and 750 mg at bedtime for a total of 1,500 mg, followed by 26 days of ganaxolone oral suspension 1,000 mg at dinner time and a taper over 4 days.

For all OL groups, if the subject experiences untoward effects the investigator has the flexibility to adjust the dose amount and/or timing of dosing by reducing the dose to a lower level and then possibly increasing it later if tolerance to the untoward effects develops.

3.2   DBPC Part

Group 1: Approximately 100 women with PPD, 18 to 48 years of age, will be screened to randomize 50 subjects in a 1:1 ratio to receive ganaxolone or matching placebo for 14 days followed by a 14-day follow-up period. The targeted ganaxolone plasma concentrations and the final dosing formulations for the DBPC part will be decided upon based on safety and efficacy results from the OL safety part and on recommendations by the DRC. Additional information for the dose selection for the DBPC part may be obtained from the ongoing phase 2A study of the ganaxolone IV formulation for PPD (conducted under IND No. 106104). The total daily dose will not exceed 1600 mg.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

Optional Group 2: After evaluation of the Group 1 DBPC data by a Data Review Committee (DRC), an additional approximately 50 women with PPD may be randomized 1:1 to be treated with ganaxolone or placebo for 14 days followed by a 14-day follow-up period. The daily dose may be lower, higher, or the same as in Group 1. However, the total daily dose will not exceed 1600 mg and no single dose will be higher than 675 mg.

In both groups, randomization will be stratified by the use of concomitant antidepressants.

4.   TREATMENT GROUPS AND STUDY ENDPOINTS

4.1   Treatment Group Comparisons

For the OL safety part of the trial, informal descriptive comparisons will be made across dosing groups. For the DBPC part, ganaxolone and placebo will be statistically compared within groups.

4.2   Study Endpoints

4.2.1   Primary Efficacy Endpoint

The primary efficacy endpoint is change from baseline in HAMD17 total score, assessed at Day 10 for the DBPC part and at the visit at end of treatment for the OL part of the trial.

4.2.2   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 ganaxolone in treating PPD:

- Change from baseline in HAMD17 total score other than at the primary endpoint time point
- 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 total score
- CGI-I scale

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

PD

4.2.4 Safety Endpoints

Safety endpoints for the OL TID, OL QHS, and DBPC groups will be:

- Incidence, relationship to investigational product (IP), severity, and seriousness of AEs throughout the trial
- Changes from baseline to Day 10 and 17 in laboratory measurements
- Changes from baseline to Day 4, 7, 10, 17, and 38 in vital signs
- Changes from baseline to Day 10, 17, and 38 in weight and body mass index (BMI)
- Change from baseline to Day 4, 7, 10, 17, and 38 in CSSRS
- Change from baseline to Day 7 and 10 in ECG parameters
- Change from baseline to Day 4, 7, 10, 17, and 38 in SSS
- Changes from baseline to Day 10 in physical examination evaluations

Safety assessments for the OL QHS 4-week group will be:

- Incidence, relationship to IP, severity, and seriousness of AEs throughout the trial
- Changes from baseline to Day 15, 29, 36, and 59 in laboratory measurements
- Changes from baseline to Day 2, 8, 15, 22, 29, 36, 59, 89, and 119 in vital signs
- Changes from baseline to Day 29 and 119 in weight and BMI
- Change from baseline to Day 2, 8, 15, 22, 29, 36, 59, 89, and 119 in CSSRS
- Changes from baseline to Day 15, 29, and 36 in ECG parameters
- Change from baseline to Day 2, 8, 15, 22, 29, 36, 59, 89, and 119 in SSS
- Changes from baseline to Day 29 in physical examination evaluations

Safety assessments for the OL 1125 mg and OL Bolus-Oral groups will be:

- Incidence, relationship to IP, severity, and seriousness of AEs throughout the trial
- Changes from baseline to Day 15, 29, 36, and 71 in laboratory measurements
- Changes from baseline to Day 2, 8, 15, 22, 29, 36, 57, and 71 in vital signs
- Changes from baseline to Day 15, 29 and 71 in weight and BMI
- Change from baseline to Day 2, 8, 15, 22, 29, 36, 57, and 71 in CSSRS
- Changes from baseline to Day 2, 8, 15, 29, and 36 in ECG parameters
- Change from baseline to Day 2, 8, 15, 22, 29, 36, 57, and 71 in SSS

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

- Changes from baseline to Day 29 in physical examination evaluations

4.2.5   PK Parameters

PK parameters will be detailed in a separate SAP if PK analyses are to be done.

5.   SAMPLE SIZE

With a sample size of 50 subjects per treatment group, the DBPC part of the trial will be able to detect a medium effect size (Cohen's d) with 93% power using a two-sided significance level of 0.05.

6.   TREATMENT ASSIGNMENT, BLINDING, AND UNBLINDING

6.1   Treatment Assignment

Eligible subjects for the OL safety part of the trial will be sequentially assigned to dosing groups as they are enrolled into the study.

Eligible subjects for the DBPC part will be randomized in a 1:1 ratio to receive either ganaxolone or placebo. Randomization will be stratified by use of concomitant antidepressant medication. The randomization scheme will be executed 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).

6.2   Blinding

The placebo infusion and placebo capsules are identical to the ganaxolone infusion and 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 the DBPC part of the trial. Members of the DRC will be unblinded. 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.

6.3   Unblinding

In the event of a medical emergency in an individual subject for which knowledge of the IP is critical to the subject's management, the blind for that subject may be broken by the treating physician. Unblinding will be managed via the IxRS.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the information is necessary; i.e., that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the IP, the problem may be properly managed without unblinding, by assuming that the subject is receiving active product.

7.   ANALYSIS POPULATIONS

The following analysis populations are defined for the trial:

Screened set: Subjects who signed an informed consent.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

Randomized set: Subjects who were randomized into the DBPC part of the trial.

Safety set: Subjects who were dispensed IP or who received an IV bolus of IP. For the DBPC part of the trial, subjects will be summarized and analyzed per treatment actually dispensed (or received), regardless of their randomization assignment.

Modified Intent-to-Treat (mITT) set: Subjects in the DBPC part of the trial who are in the safety set and who have at least one post-baseline observation for HAMD17 total score. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment actually received.

Per protocol set: Subjects in the mITT set who do not have protocol deviations that could affect treatment group comparisons on key efficacy endpoints. A list of subjects with protocol deviations that preclude them from being in the per protocol population will be compiled prior to database lock.

8.   REPORTING AND ANALYSIS CONVENTIONS

8.1   Programming Environment

SAS® version 9.3 or higher (SAS Institute, Cary, North Carolina) will be used for statistical analyses and the production of tables, figures, and listings (TFLs).

8.2   Reporting Conventions

Tables of contents for TFLs to be produced are shown in Appendix B. Separate sets of TFLs will be produced for the OL safety and DBPC parts of the trial. Separate tables and figures may be produced within parts of the trial for visit-based assessments where visit schedules differ; e.g., the OL QHS 4-week dosing group has a different visit schedule than the OL TID and OL QHS dosing groups and may therefore be presented in a separate set of tables and figures. TFLs will be appended to the final CSR.

TFLs will be displayed in landscape orientation unless the presentation is easier to interpret in portrait mode. TFLs displayed in-text in the CSR will be in portrait mode.

Fonts are to be Times New Roman or Arial only. Font size is to be no smaller than 9pt.

Titles and footnotes must appear on every page of the TFL. Titles on pages other than the first page must indicate that the TFL is a continuation of the first page (e.g., "(cont'd)" at the end of the first title line). Titles should be as short as possible, ideally 126 characters or less. Footnotes should be used sparingly and must add value to the TFL. If more than four footnote lines are planned then a cover page may be used to display footnotes. Superscripts are not to be used in TFL titles.

Cells with missing values for either numeric or character variables will be populated with an indicator for missingness (e.g., "—").

All date values will be presented as DDMMMYYYY (e.g., 29AUG2001) format. A four-digit year is preferred for all dates. All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds should only be reported if they were measured as part of the study.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

TFLs will have the name of the program, the data source, and a date/time stamp on the bottom of each page. There will be a 1:1 relationship between programs and TFLs; i.e., each program will output one and only one TFL.

Tables and figures will present data summaries and/or analyses for the appropriate study population; e.g., summaries of safety parameters will be shown for the safety set only. Treatment group order in tables and figures for the OL safety part of the trial will be OL TID, OL QHS, OL QHS 4-week; some tables and figures may also display "All Subjects." Treatment group order in tables and figures for the DBPC part will be Ganaxolone, Placebo; some tables and figures may also display "All Subjects." Tables and figures will present summaries/analyses by study visit or analysis visit window, as appropriate. Table column headers and figure legends will include subgroup sample sizes ("N = xx"). Sample sizes reported as part of descriptive statistics ("n") will be the number of non-missing observations.

Listings will present all data collected for the OL safety set and for the randomized set, unless otherwise noted below. Listings will be ordered by unique subject identifier, date, data collection time if applicable, nominal study visit, and analysis visit window if applicable (see Section 8.7).

8.3   General Analysis Conventions

Categorical variables will be summarized using frequencies and percentages in each category for which there was at least one response. Percentages will be reported to one decimal place. Unless otherwise noted in Section 11, categorical variables will be analyzed using chi square tests of association or, if any contingency table cell has less than 5 subjects, Fisher's exact test.

Continuous variables will be summarized using descriptive statistics (e.g., n, mean, standard deviation, least-squares mean with standard error, distribution percentiles). The number of decimal places for minimums and maximums will be the same as the original data. The number of decimal places for means, medians, and interquartile ranges will be the same as the original data plus one. The number of decimal places for measures of variance will be the same as the original data plus two. Unless otherwise noted in Section 11, continuous variables will be analyzed using t-tests or, if appropriate, analysis of covariance with baseline as a covariate. Non-parametric tests and data transformations will be considered for variables with distributions that violate parametric assumptions.

Data with qualifiers (e.g., "<") will be listed with but summarized without the qualifier.

P-values will be presented in summary tables to two decimal places if > 0.01, to three places if < 0.01 but > 0.001, and to four places if < 0.001 but > 0.0001. However, p-values > 0.045 but < 0.055 will also be presented to three decimal places. P-values < 0.0001 will be presented as "< 0.0001."

Statistical tests will be two-sided and tested at the 0.05 significance level unless otherwise noted in Section 11.

8.4   Subgroups

There are no planned analyses by subgroups.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

8.5   Missing Data

Listings will present data as reported. Missing or partially missing dates that are required for date-dependent definitions (e.g., treatment-emergent AEs, concomitant medications) will be assumed to be the most conservative date possible. For example, an AE with a completely missing start date will be considered treatment-emergent; similarly, an AE that started the same month and year as date of first dose of IP but with missing start day will be considered treatment-emergent. Handling of missing observations for the primary efficacy endpoint is described in Section 11.2.6.

8.6   Study Period and Time Point Definitions

The following study periods and time points are defined:

Screening Period: the 1- to 14-day time period before day of enrollment for the OL safety part of the trial or day of randomization for the DBPC part.

Baseline Observation: for a given parameter for a given subject, the last observation before the first dose of IP or planned first dose of IP if not dosed.

Study Day 1: for a given enrolled subject, the day of actual first dose of IP or planned first dose of IP if not dosed.

(Nominal Visit) Analysis Time Point: analysis based on data collected at the *(nominal visit)* time point, where nominal visits are as shown below in Section 8.7.

End of Study (EOS), Subject Level: the date of completion of the last planned study visit or date of discontinuation for any reason.

EOS, Study-Level: the date when all enrolled subjects in the OL safety part of the trial and all randomized subjects in the DBPC part have reached subject-level EOS.

8.7   Visit Windows

Visit windows will be based on study day of the observation and Study Day 1; specifically:

- On or after Study Day 1: study day = date of observation – Study Day 1 date + 1

- Before Study Day 1: study day = date of observation – Study Day 1 date

For subjects in the screened set who were not enrolled or for subjects who otherwise did not have a planned date of first dose, all observations belong to the screening visit analysis window.

If multiple valid, non-missing observations exist within a given window, the observation to be used will be:

1. the observation closest to the nominal visit day in question, or

2. the latest observation if the multiple observations are equidistant from the nominal visit day, or

3. the average (arithmetic or geometric, as appropriate) of the observations if the multiple observations have the same actual time point. In instances of multiple observations with the same time point from different laboratories, only observations from the central laboratory will be used.

For PK analyses, actual dates and times will be used.

8.7.1   OL TID, OL QHS, and DBPC Windows

Visit windows per protocol and to be used in listings, summaries and analyses for the OL TID, OL QHS, and DBPC groups are as follows:

Nominal Visit	Nominal Day	Min Day Per Protocol	Max Day Per Protocol	Min Day for Analyses	Max Day for Analyses
Screening	--	-14	-1	-14	-1
Day 1	1	1	1	1	1
Day 4	4	4	6	2	6
Day 7	7	7	9	7	9
Day 10	10	10	13	10	13
Day 17	17	15	19	14	27
Day 38	38	34	42	28	48

8.7.2   OL QHS 4-Week Windows

Visit windows per protocol and to be used in listings, summaries and analyses for the OL QHS 4-week group are as follows:

Nominal Visit	Nominal Day	Min Day Per Protocol	Max Day Per Protocol	Min Day for Analyses	Max Day for Analyses
Screening	--	-14	-1	-14	-1
Day 1	1	1	1	1	1
Day 2	2	2	2	2	5
Day 8	8	8	8	6	11
Day 15	15	15	15	12	18
Day 22	17	15	19	19	23
Day 29	29	29	29	24	32
Day 36	36	34	38	33	47
Day 59	59	57	61	48	74
Day 89	89	85	93	75	104
Day 119	119	115	123	105	133

8.7.3   OL 1125 mg and OL Bolus-Oral Windows

Visit windows per protocol and to be used in listings, summaries and analyses for the OL 1125 mg and OL Bolus-Oral groups are as follows:

Nominal Visit	Nominal Day	Min Day Per Protocol	Max Day Per Protocol	Min Day for Analyses	Max Day for Analyses
Screening	--	-14	-1	-14	-1
Day 1	1	1	1	1	1
Day 2	2	2	4	2	4

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

Day 8	8	5	11	5	11
Day 15	15	12	18	12	18
Day 22	17	19	25	19	25
Day 29	29	26	32	26	32
Day 36	36	33	39	33	47
Day 57	59	54	60	48	64
Day 71	89	68	74	65	77

9.   STUDY POPULATION

Summaries of study population parameters will be done for the safety set unless otherwise noted. The study population will be described by the parameters below.

9.1   Analysis Populations

The analysis populations defined in Section 7 will be described in terms of the identification of subjects in each population and the frequency distribution of each population. Summaries will be done for the OL safety set (OL safety part) and for the randomized set (DBPC part).

9.2   Eligibility and Informed Consent

Eligibility and informed consent parameters will be listed and will include protocol version (date), date of informed consent, inclusion and/or exclusion criteria that were not met, whether or not the subject was a previous screen failure and, if so, date of previous screen and previous subject number. Satisfaction of inclusion/exclusion criteria will be summarized.

9.3   Baseline Characteristics

Demographic and other baseline characteristics will be listed and summarized and will include study site, age, race, and ethnicity. Age will be computed in SAS as follows:

$$AGE = floor((intck('MONTH', bdt, rdt) - (day(rdt) < day(bdt))) / 12)$$

where bdt = birth date in SAS date format and rdt = Study Day 1 date in SAS date format. For the DBPC group, data will be summarized for both the safety set and the mITT set.

9.4   Medical History

Medical history will be listed and summarized. Reported medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.1, to a System Organ Class (SOC) and Preferred Term (PT). A summary will be produced showing number and percentage of subjects with each PT within SOCs.

9.5   Mini Neuropsychiatric Interview v7.0 (MINI)

MINI results will be listed; namely, whether or not the assessment was performed, date and time of the assessment, whether or not the subject met the inclusion criterion for major depressive episode per the MINI, and other psychiatric diagnosis per the MINI.

9.6 State versus trait; Assessability; Face Validity; Ecological Validity; and Rule of 3 Ps (SAFER) Interview

SAFER results will be listed; namely, whether or not the assessment was performed, date and time of the assessment, and whether or not the subject met the inclusion criteria for diagnosis of PPD and severity of depression per the SAFER.

9.7 Clinical Global Impression – Severity (CGI-S) Scale

The CGI-S is a clinician-rated 7-point scale to assess severity of a subject's depression relative to the clinician's past experience with subjects who have the same diagnosis. CGI-S will be done only at screening and on Day 1. Possible responses are: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7= extremely ill. Observed values will be listed, and frequencies and percentages of subjects at each response level will be summarized.

9.8 Subject Study Progress

A listing of subject study progress will show dates of screening, informed consent, study visits, and EOS. Number of subjects who completed each milestone and visit will be summarized.

9.9 Subject Disposition

A listing of subject disposition will include dates of randomization (DBPC part only), first dose of IP, last dose of IP, and EOS; and reasons for IP and/or study discontinuation (if applicable). Frequencies and percentages of subjects who discontinued the IP and/or study will be summarized. Reasons for discontinuation will also be summarized.

10. TREATMENTS

Treatment parameters will be listed and summarized for the safety set. Some or all summaries may also be done for other analysis populations defined in Section 7. Treatment parameters are described below.

10.1.1 IP Exposure

A listing of IP exposure will include IV bolus infusion start/stop date/times and infusion rate (OL Bolus-to-Oral group only), number of capsules dispensed, number of capsules returned, mean daily dose (mg), duration of exposure, and percent compliance. Duration of exposure will be calculated as:

$$\text{days of exposure} = \text{date of last dose} - \text{date of first dose} + 1.$$

Percent compliance at a given visit will be calculated as:

percent compliance = (number of capsules ingested) / (number of expected capsules ingested) x 100

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

where number of capsules ingested will be calculated as the number of capsules dispensed at the prior visit minus the number of capsules returned at the given visit.

Mean daily dose, duration of exposure, and percent compliance will be listed and summarized for each post-baseline visit as well as cumulatively over the total dosing period. A listing will also be provided of subjects who has dose adjustments (i.e., deviations from the scheduled titration scheme), and dose adjustments will be summarized.

11. EFFICACY ANALYSIS

Summaries of efficacy parameters will be done for the safety set from the OL safety part of the trial and for the mITT set. Statistical analyses will primarily be done for the mITT set. Some or all summaries and/or analyses may also be done for other analysis populations defined in Section 7.

For the OL safety part of the trial, referring to efficacy endpoints as "primary," "secondary," and "exploratory" is related to the degree of influence each type of endpoint is expected to have on decision-making rather than to considerations associated with inferential analysis (such as control of type 1 error). The primary time point of interest for all efficacy parameters will be Day 10 for the DBPC part of trial and the visit at end of treatment (before initiation of taper) for the OL safety part.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

11.1 Efficacy Parameters

11.1.1 HAMD17

The HAMD17 is a 17-item clinician-rated instrument used to assess the range of symptoms associated with major depression and will be done at every study visit. Items are scored either from 0 to 2 or 0 to 4, depending on the item, and a total score is derived by summing over all 17 items. Observed values, changes from baseline, "response," and "remission" based on the total score will be listed and summarized. "Response" is defined as $\geq$ 50% decrease from baseline. "Remission" is defined as an observed total score of 0 to 7 (note: HAMD17 total score must be $\geq$ 18 at randomization). The listing will also include observed values and changes from baseline for each of the 17 items. Improvement is indicated by negative change scores and this will be footnoted in TFLs.

11.1.2 EPDS

The EPDS is a 10-question self-rated instrument used to assess symptoms of PPD and will be administered at every study visit. Items are scored from 0 to 3 with a total score derived by summing over all 10 items. Observed values and changes from baseline based on the total score will be listed and summarized. The listing will also include observed values and changes from baseline for each of the 10 items. Improvement is indicated by negative change scores and this will be footnoted in TFLs.

An Obsessive Thoughts questionnaire, comprised of two questions scored from 0 to 4, is an add-on to the EPDS but will not be included in the EPDS total score for analysis. A listing and summary table will be provided.

11.1.3 STAI6

The STAI6 is a 6-question self-rated instrument used to assess anxiety state and will be administered at every study visit. Items are scored from 1 to 4 with a total score derived by summing over all 6 items and multiplying by 20/6. Observed values and changes from baseline based on the total score will be listed and summarized. The listing will also include observed values and changes from baseline for each of the 6 items. Improvement is indicated by negative change scores and this will be footnoted in TFLs.

11.1.4 CGI-I

The CGI-I is a clinician-rated 7-point scale to assess degree of improvement from baseline and will be done at every post-baseline study visit. Possible responses are: 1 = very much improved 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse. Observed values will be listed, and frequencies and percentages of subjects at each response level will be summarized. Both original scores as well as scores dichotomized as "very much or much improved" (response = 1 or 2) vs. all other responses (3-7) will be analyzed.

11.2 Statistical Methods

11.2.1 Primary Efficacy Endpoint

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

The primary efficacy endpoint will be HAMD17 total score change from baseline, assessed at Day 10 for the DBPC part and at the visit at end of treatment for the OL safety part of the trial.

The null (H_o) and alternative (H_A) hypotheses will be:

$$H_o: \Delta_G - \Delta_P = 0$$

$$H_A: \Delta_G - \Delta_P \neq 0$$

where Δ_G and Δ_P are mean change from baseline to Day 10 in HAMD17 total score in ganaxolone and placebo groups, respectively. Rejection of H_o at a 0.05 significance level will be considered successful demonstration of efficacy. Analysis will be done using a "mixed model" for repeated measures (MMRM) as described below. For the effect of interaction between treatment and day, the estimated treatment group difference in least squares (LS) means at Day = 10, along with the associated p-value, will be reported.

11.2.2 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 ganaxolone in treating PPD:

- Change from baseline in HAMD17 total score other than at the primary endpoint time point

- 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 total score

- CGI-I

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

11.2.4 Method of Analysis for Longitudinal Continuous Endpoints

Treatment group comparisons on endpoints that are continuous variables assessed longitudinally will be done using MMRM with change from baseline as the dependent variable; nominal visit (day), treatment group, and treatment-by-day interaction as fixed effects; baseline observation as a fixed-effect covariate; and correlated errors within subject. Use of concomitant antidepressants will also be considered as a fixed-effect covariate since it is a randomization stratification factor. Covariance estimation will be done using restricted maximum likelihood.

Error degrees of freedom will be calculated using the Kenward-Rogers approximation. Unstructured covariance for the residuals (R matrix) will initially be specified but other covariance structures may be explored by examining the R matrix and using goodness-of-fit measures (e.g., Akaike's Information Criterion (AIC)). If a structured covariance is used, the sandwich estimator will be used for standard errors and error degrees of freedom will be calculated using the between-within method. Model-based LS means will be reported for each treatment group, along with p-values for treatment group comparisons, for each nominal visit. A p-value for treatment group comparison over all visits will only be reported if there does not appear to be a treatment-by-day interaction, either based on the interaction p-value or by a descriptive examination of the data, and the term for treatment-by-day interaction will not be included in the model.

Model assumptions will be evaluated using diagnostic tools such as Q-Q and scatter plots of residuals, and sensitivity analyses using alternative methods (e.g., rank-based, analysis of covariance (ANCOVA) at individual time points) will be considered if there appear to be substantial deviations from model assumptions. Outlier assessment will be done using visual inspection (e.g., box-and-whisker plots) and potential outliers will be investigated for data entry accuracy and biological consistency. If unexplainable outliers are present for the primary efficacy endpoint, a sensitivity analysis will be done excluding the outliers to assess their effect on the efficacy conclusion.

11.2.5 Method of Analysis for Longitudinal Ordinal Endpoints

Treatment group comparisons on ordinal (including binary) endpoints assessed longitudinally will be done using generalized estimating equations (GEE) with nominal visit (day) and treatment group as main effects, treatment-by-day as an interaction term, an appropriate baseline value as a covariate, where applicable; and correlated errors within subject. Use of concomitant antidepressants will also be considered as a covariate.

The working correlation structure will initially be specified as unstructured but other structures may be explored by examining the covariance matrix and using goodness-of-fit measures (e.g., Quasilikelihood under the Independence model Criterion (QIC)). P-values for treatment group comparisons will be reported for each nominal visit. A p-value for treatment group comparison

over all visits will only be reported if there does not appear to be a treatment-by-day interaction, either based on the interaction p-value or by a descriptive examination of the data, and the term for treatment-by-day interaction will not be included in the model.

Alternative approaches for the analysis of ordinal endpoints may be considered and will include the Cochran-Mantel-Haenszel (CMH) row mean scores test using rank scores, chi square tests of association, and Fisher's exact test.

11.2.6 Missing Observations

One of the assumptions of MMRM for longitudinal continuous variables is that missing observations are missing at random (MAR), i.e., missingness is unrelated to the missing variable but can be related to another variable on which data have been collected. Because this assumption is not testable, and because it seems possible that subjects with poorer outcomes may be more likely to miss trial assessments, a sensitivity analysis under a missing-not-at-random (MNAR) assumption may be done for any endpoint but will be done for the primary efficacy endpoint if change-from-baseline observations for HAMD17 total score are missing at any time point for at least 10% of subjects. For the MNAR model, the imputation will be based only on subjects randomized to placebo. The imputation method will be fully conditional specification (FCS) regression with 25 imputations. The imputer's model will include observed values at each time point included in the MMRM analysis, including baseline.

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 using FCS logistic regression as the imputation method.

11.2.7 Multiplicity

There will be no adjustments for type 1 error inflation due to multiplicity.

12.   SAFETY PARAMETERS

Listings and summaries of safety parameters will be done for the safety set. Some or all summaries may also be done for other analysis populations defined in Section 7.

12.1   AEs

AEs reported from screening through EOS will be coded according to MedDRA® version 19.1 or greater. Each reported AE will be mapped to a PT and 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 interruption or discontinuation (excluding deaths), or dose reduction. Listings will include reported term, PT, and SOC; start and stop date; outcome; whether or not the AE was serious;

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

severity; whether or not the AE was related to IP; whether or not the AE caused the subject to discontinue from the study; and action taken.

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 relationship will be considered related and missing severity will be considered severe. 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.

12.2 Safety Laboratory Measurements

Specific laboratory measurements to be obtained are detailed in Section 7 of the protocol. Collection will be done at select visits (see Appendix A). Listings of safety laboratory measurements will include normal ranges, observed values with out-of-range values flagged, and changes from baseline.

Observed values and changes from baseline will be summarized. A separate series of summaries will show incidence of out-of-range observations. Shift tables will summarize shifts from one out-of-range category at baseline to another out-of-range category at each subsequent study visit.

Listings and summaries will be done separately for each of the following groups of laboratory measurements:

- Biochemistry
- Hematology
- Urinalysis
- Urine pregnancy test
- Urine drug screen

12.3 Vital Signs, Height, Weight, and Body Mass Index (BMI)

Vital signs will include systolic and diastolic blood pressure, pulse rate, respiration rate, and body temperature and will be measured at every study visit. Any abnormal screening vital sign results considered to be clinically significant should be repeated to confirm the finding. Height will be measured at the screening visit. Weight will be collected at select visits (see Appendix A). Listings of vital signs, height, weight, and BMI will include observed values and changes from baseline. BMI will be calculated as:

$$BMI = \frac{weight\ (kg)}{(height\ (m))^2}$$

12.4 CSSRS

The CSSRS is a clinician-rated assessment of suicidality and will be done at every study visit. The CSSRS consists of three sections: Suicide Ideation, Intensity of Ideation, and Suicide Behavior. The Suicide Ideation section consists of 5 questions and proceeds as follows:

1. Ask Questions 1 and 2.
2. If Question 1 and 2 are negative, proceed to the Suicide Behavior section.
3. If the answer to Question 1 and/or 2 is "yes," complete the Intensity of Ideation section.
4. If the answer to Question 2 is "yes," ask Questions 3-5, then proceed to the Suicide Behavior section.
5. If the answer to Question 2 is "no," proceed to the Suicide Behavior section.

CSSRS responses will be listed and summarized.

12.5   12-Lead ECG

12-lead ECG will be performed at select visits (see Appendix A). The ECG vendor will provide an external database. Observed values and changes from baseline for continuous ECG parameters (e.g., heart rate, PR interval, QRS complex, QTcF) will be listed and summarized. Interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) and specification of abnormalities will also be listed and summarized.

12.6   SSS

The SSS is an 8-item self-rated scale designed to measure level of sleepiness and will be administered at every study visit except screening. Possible responses range from 1 ("Feeling active, vital, alert, or wide awake") to 8 ("asleep"). Observed values will be listed and summarized.

12.7   Physical Examination

Physical examinations will be conducted at screening and at Day 10 (OL TID, OL QHS, and DBPC groups) or at Day 29 (OL QHS 4-week, OL 1125 mg, and OL Bolus-Oral groups). The listing will include the overall assessment of the examination (normal or abnormal) and abnormalities, if any, for each body system. Findings will be summarized either as frequencies of normal/abnormal indicators or, if appropriate (i.e., if data are not too sparse), as shifts from baseline in normal/abnormal indicators for each body system.

13.   OTHER DATA COLLECTED

13.1   Neurosteroid Levels

Blood samples for determination of neurosteroid levels (allopregnanolone and potentially other metabolites of progesterone) will be collected at select visits (see Appendix A). Data will be listed, summarized, and/or analyzed by a third-party vendor.

13.2   Laboratory Sample Collection

A listing of laboratory sample collection dates, times, and accession numbers will be provided and will include PK collection data as well.

13.3   Protocol Deviations

In addition to the listing of eligibility detailed in <u>Section 9.2</u>, a separate listing will show all other protocol deviations and will include protocol version, the category of the deviation (to be determined), and an indicator for per protocol exclusion (DBPC part only), to be determined on a case-by-case basis before database lock. Frequency and percentage of subjects in each deviation category and excluded from the per protocol population will be summarized.

14.   SEQUENCE OF PLANNED ANALYSES

14.1   Safety Reviews

During the OL safety part of the trial, the sponsor will review safety data after completion of each dosing group and before beginning randomization for the DBPC part. The DRC will review safety data from Group 1 of the DBPC part before beginning randomization for Group 2 (if applicable).

14.2   Administrative Interim Analyses

The sponsor may perform administrative interim analyses, including public release of top line results, at any time during the OL safety part of the trial, for the purpose of planning subsequent clinical trials.

14.3   Final Analysis of the OL Safety Part

Final analysis of the OL safety part will occur when all OL subjects have reached EOS, 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 have been identified, and the database for the OL safety part has been locked.

The sponsor may decide to stop the study, or make the data public, after completion of the OL safety part.

14.4   Final Analysis of the DBPC Part

Final analysis of Group 1 of the DBPC part will occur when all DBPC subjects from Group 1 have reached EOS, 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 population have been identified, and the database for Group 1 has been locked.

Final analysis of Group 2 of the DBPC part (if applicable) will occur when all DBPC subjects from Group 2 have reached EOS, 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 population have been identified, and the database for Group 2 has been locked.

The sponsor may decide to stop the study, or make the data public, after completion of Group 1 of the DBPC part.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

15. DRC

After completion of Group 1 of the DBPC part, the data will be evaluated by an independent DRC. Based on the analysis and recommendation by the DRC, at that point the study may be closed or may proceed to randomize Group 2 of the DBPC part. A separate guidance document will outline the functions and membership of the DRC.

Data on the following, in the form of TFLs and/or narratives, will be provided to the DRC for review:

- Subject disposition
- Demographic and other baseline characteristics
- Ganaxolone exposure
- Treatment-emergent AEs and SAEs
- Safety laboratory evaluations
- Vital signs
- HAMD17
- EPDS
- STAI6

16. DEVIATIONS FROM THE PROTOCOL

Protocol	Deviation
CGI-S mentioned in efficacy objective	CGI-S is not an efficacy endpoint (it is not assessed post-baseline)
Safety set: all subjects who received IV IP.	Safety set: Subjects who were dispensed IP or who received an IV bolus of IP.
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 Per-Protocol Set will consist of all subjects in the mITT set who do not have protocol deviations that may affect key efficacy endpoints.
mITT set: all subjects in the DBPC part of the trial who received IP and who have at least 1 post-baseline HAMD17 assessment.	mITT set: Subjects in the DBPC part of the trial who are in the safety set and who have at least one post-baseline observation for HAMD17 total score.
The dosing, treatment duration and timing of evaluations for the double-blind portion of the study will be decided based on the results of the Open Label Part and recommendations of the Data Review Committee (DRC).	An independent DRC will be in place for the DBPC part only.

REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), September 1998.

2. ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April, 2018. http://www.amstat.org/ASA/Your-Career/Ethical-Guidelines-for-Statistical-Practice.aspx.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), November 1995.

4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Good Clinical Practice (E6), April 1996.

5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, General Considerations for Clinical Trials (E8), July 1997.

6. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), September 1998.

7. Johnson JR, Fitts D. Statistical Analysis Plans: Principles and Practice. Workshop Number 8. Presented at the Society for Clinical Trials 2007 Annual Meeting Montreal, Canada Sunday May 20, 2007. http://docshare01.docshare.tips/files/9381/93818340.pdf.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

APPENDIX A: SCHEDULES OF ASSESSMENTS

OL TID, OL QHS, and DBPC

VISIT	Screening (V1)	Day1 (V2)	Day4 (V3)	Day7 (V4)	D10 (V5)	Day17 (V6, 1st FU)	Day38 (V7, 2nd FU)
Informed consent	X						
Demographics, medical history	X						
MINI neuropsychiatric interview	X						
Inclusion/Exclusion criteria	X	X					
Randomize patient (DB only)		X					
Dispense medication		X	X	X	X		
Concomitant Medications and Prior Therapy Review	X	X	X	X	X	X	X
Physical examination	X				X		
SAFER Interview (during screening)	X						
Vital signs (BP, Pulse, RR, temperature)	X	X	X	X	X	X	X
Height (screening only) and weight	X	X			X	X	X
ECGs	X	X		X	X		
Safety Laboratory Tests	X	X			X	X	
Neurosteroid sample collection		X			X	X	
Urine Drug Screen and Pregnancy Tests	X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X
PK sample collection			X	X	X	X	X
HAMD17	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X
CGI-S	X	X					
EPDS	X	X	X	X	X	X	X
STAI6	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X
SSS		X	X	X	X	X	X
Start Taper					X		

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 10) neurosteroid sample 11) PK sample 12) urine drug screen and pregnancy test 13) physical examination. SAFER interview is scheduled if subject meets the eligibility criteria at the Screening visit. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study. Screening period may be extended to 21 days with approval from the medical monitor.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

OL QHS 4-Week

VISIT	Screening (V1)	Day1 (V2)	Day2 (V3)	Day8 (V4)	D15 (V5)	Day22 (V6)	Day29 (V7)	Day36 (V8; 1st FU)	Day59 (V9; 2nd FU)	Day89 (V10; 3rd FU)	Day 119 (V11; 4th FU)
Informed consent	X										
Demographics, medical history	X										
MINI neuropsychiatric interview	X										
Inclusion/Exclusion criteria	X	X									
Randomize patient (DB only)		X									
Dispense medication / Return Accountability		X	X	X	X	X	X	X			
Concomitant Medications and Prior Therapy Review	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X						X				
SAFER Interview (during screening)	X										
Vital signs (BP, Pulse, RR,	X	X	X	X	X	X	X	X	X	X	X
Height (screening only) and weight	X	X					X				X
ECGs	X				X		X	X			
Safety Laboratory Tests	X	X			X		X	X	X		
PK sample collection			X	X	X		X	X	X		
Neurosteroid sample collection		X	X	X	X		X	X	X		
Urine Drug Screen and Pregnancy Tests	X	X		X	X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X	X	X	X
HAMD17	X	X	X	X	X	X	X	X	X	X	X
CGI-I		X	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
STAI6	X	X	X	X	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X	X	X	X	X
SSS		X	X	X	X	X	X	X	X	X	X
Start Taper							X				

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 10) neurosteroid sample 11) PK sample 12) urine drug screen and pregnancy test 13) physical examination. SAFER interview is scheduled if subject meets the eligibility criteria at the Screening visit. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study. Screening period may be extended to 21 days with approval from the medical monitor.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

OL 1125 mg and OL Bolus-Oral

VISIT	Screening (V1)	Day1 (V2)	Day2 (V3)	Day8 ±3d (V4)	D15 ±3d (V5)	Day22 ±3d (V6)	Day29 ±3d (V7)	Day36 ±3d (V8; 1st FU)	Day57 ±3d (V9; 2nd FU)	Day71 ±3d (V10; 3rd FU)
Informed consent	X									
Demographics, medical history	X									
MINI neuropsychiatric interview	X									
Inclusion/Exclusion criteria	X	X								
Dispense medication / Return Accountability		X	X	X	X	X	X	X		
Concomitant Medications and Prior Therapy Review	X	X	X	X	X	X	X	X	X	X
Physical examination	X						X			
SAFER Interview (during screening)	X									
Vital signs (BP, Pulse, RR,	X	X	X	X	X	X	X	X	X	X
Height (screening only) and weight	X	X			X		X			X
ECGs	X	X	X	X	X		X	X		
Safety Laboratory Tests	X	X			X		X	X		X
[b] Bolus (OL Bolus-Oral group only)		X								
PK sample collection			X	X	X	X	X	X		
PK subgroup sample collection		[c] X								
Neurosteroid sample collection		X	X	X	X		X	X		X
Urinalysis, Drug Screen and Pregnancy	X	X		X	X	X	X	X	X	X
Record AEs		X	X	X	X	X	X	X	X	X
[a] HAMD17	X	X	X	X	X	X	X	X	X	X
CGI-I			X	X	X	X	X	X	X	X
CGI-S	X	X								
EPDS	X	X	X	X	X	X	X	X	X	X
STAI6	X	X	X	X	X	X	X	X	X	X
CSSRS	X	X	X	X	X	X	X	X	X	X
SSS		X	X	X	X	X	X	X	X	X
Start Taper							X			

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

[a] CTNI will conduct all HAMD ratings except the one at screening

[b] IV bolus is to be done at approximately 4 pm (preferably within ±1 hour) and allowing for at least 1-hour post-bolus follow-up at the site before discharge

[c] A sub-group of 6 subjects (to be called 'PK sub-group') in each of the OL 1,125 mg and OL Bolus-Oral groups will stay overnight on the unit between Day 1 and Day 2 to undergo comprehensive PK assessment as follows: for the OL 1,125 mg group plasma samples for PK analysis will be drawn at the following times after the first oral dose on Day 1 (e.g., the 675 mg oral capsules dose at 7 pm at dinner time; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the 10 pm 675 mg dose), at +4hr, +5hr, +6hr, and at 8 am on Day 2. For the OL Bolus-Oral group plasma samples for PK analyses will be drawn at the following times after the IV bolus on Day 1 (e.g., the 12 mg IV bolus at 4 pm; 0hr): +1hr, +2hr, +3hr (i.e., just prior to the first oral dose of 750 mg oral suspension at dinner time), at +4hr, +5hr, +6hr (i.e., just prior to the second 750 mg oral suspension evening dose), at + 7hr, +8hr, and at 8 am on Day 2.

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 10) neurosteroid sample 11) PK sample 12) urinalysis, urine drug screen and pregnancy test 13) physical examination. SAFER interview is scheduled if subject meets the eligibility criteria at the Screening visit. The SAFER interview will be conducted during the screening period. The investigational site must wait for the results of the SAFER interview before enrolling the subject into the treatment phase of the study. Screening period may be extended to 21 days with approval from the medical monitor.

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

APPENDIX B: TABLES OF CONTENTS FOR TABLES, FIGURES, AND LISTINGS

TABLES

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

FIGURES

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018

LISTINGS

STUDY POPULATION

16.2.1.1	Critical Dates and Scheduled Visits
16.2.1.2	Subject Study Visits
16.2.1.3	Subject Disposition
16.2.2.1	Informed Consent
16.2.2.2	Eligibility & Randomization
16.2.2.3	Protocol Deviations
16.2.3	Analysis Populations
16.2.4.1	Demographics
16.2.4.2	Medical History
16.2.4.3.1	MINI
16.2.4.3.2	SAFER
16.2.4.3.3	CGI-S
16.2.4.4.1	Pre-Treatment AEs
16.2.4.4.2	Pre-Treatment SAEs
16.2.4.5.1	Baseline General Medications
16.2.4.5.2	Baseline Psychological Medications
16.2.4.5.3	Baseline Psychological Treatments
16.2.5.1	Investigational Product Exposure
16.2.5.2	Investigational Product Accountability & Compliance

EFFICACY

16.2.6.1	Hamilton Depression Rating Scale (HAMD)
16.2.6.2	Edinburgh Postnatal Depression Scale (EPDS)
16.2.6.3	Spielberger Trait-State Anxiety Inventory (STAI6)
16.2.6.4	Clinical Global Impression - Improvement (CGI-I)
16.2.6.5	Obsessive Thoughts

SAFETY

16.2.7.1	Treatment-Emergent Adverse Events (TEAEs)
16.2.7.2	Treatment-Emergent Serious Adverse Events (TESAEs)
16.2.7.3	TEAEs Resulting in IP Discontinuation
16.2.7.4	TEAEs Resulting in Dose Reduction or Interruption
16.2.7.5	TEAEs Resulting in Death
16.2.8.1	Biochemistry
16.2.8.2	Hematology
16.2.8.3	Urinalysis
16.2.8.4	Urine Pregnancy
16.2.8.5	Urine Drug Test
16.2.8.6	Lab Sample Collection

IND No. 135256
Protocol 1042-PPD-2003

Marinus Pharmaceuticals, Inc
Statistical Analysis Plan.
Version 1.0, November 15, 2018