DB 104-01 Statistical Analysis Plan

A Biomarker-Guided, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Liafensine in Patients with Treatment-Resistant Depression

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VERSION HISTORY

Version	Date	Changes	Rationale
0.7	04Jan2024	Draft submitted in SN 0018 for FDA review	Initial draft
1	31Jan2024	Version submitted in SN 0019 prior to early data readout Section 5.3: Updated calculation for treatment duration from weeks to days; added calculation for dosing compliance Section 5.4.3: Removed CGI-I analysis by biomarker status	Minor updates for clarity
2	18Mar2024	Version submitted in SN 0021 prior to database lock Section 4.1: Added randomized analysis set (RAS) Section 5.1.3: Added 2nd age group of < 65 and ≥ 65 Section 5.4.1.1: a. Added sensitivity analyses based on RAS to the list of sensitivity analyses b. Added clarifications that MMRM will be implemented using SAS Mixed procedure with the default REML (restricted maximum likelihood) estimation c. Listed intercurrent events (ICEs) in this study Section 5.4.1.2: a. Added use of the algorithm (Lu 2010) to assist in the convergence if the MMRM model does not converge b. Added clarifications that the LSMESTIMATE statement in SAS Mixed procedure will be used to test the global null hypothesis of no treatment difference between both active arms and placebo while keeping all 3 treatment groups separately c. Added clarifications that all available data collected from all subjects before or after ICEs will be included in the analysis unless otherwise specified d. Added clarifications that for MADRS, the total score is set to missing if 50% or more items are missing at an assessment. When this occurs, the change from baseline value will be imputed without using any of the non-missing items. e. Updated the tables and figures to assess the MAR assumption based on ICEs Section 5.4.1.3: a. Added sensitivity analyses based on RAS: a set of sensitivity analyses listed under this section will be performed using DGM4-positive patients in RAS. The same MMRM in the primary and sensitivity analyses described in the previous section of SAP	To address FDA review comments on draft SAP V0.7

Version	Date	Changes	Rationale
		will be carried out. The model will include the fixed effects of treatment, visit (categorical covariate), treatment by visit interaction, baseline MADRS total score (continuous covariate), and region. b. Grouped ICEs with corresponding strategy in one of the sensitivity analyses c. Per b above, added a hypothetical strategy for subjects on prohibited medications Section 7: Added a new reference (Lu 2010) Section 8: Added sample SAS codes	

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT (SGPT)	alanine aminotransferase (serum glutamic-pyruvic transaminase)
AST (SGOT)	aspartate aminotransferase (serum glutamic-oxaloacetic transaminase)
ATC	Anatomical Therapeutic Chemical
ATC-2	Anatomical Therapeutic Chemical (subgroup level 2)
ATRQ	Antidepressant Treatment Response Questionnaire
BP	blood pressure
CGI-I, -S	Clinical Global Impressions Scale-Improvement, -Severity
CMH	Cochran-Mantel-Haenszel
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
DESS	Discontinuation-Emergent Signs and Symptoms (scale)
DGM4	Denovo Genomic Marker 4, a genetic biomarker for DB104 (liafensine)
DILI	drug-induced liver injury
ECG	Electrocardiogram
EDC	electronic data capture (system)
EOT	End of Treatment
FAS	full analysis set
FCS	fully conditional specification
HAMD-17	Hamilton Depression Rating Scale - 17 Item
HR	heart rate
ICE	intercurrent event
IRT	interactive response technology
LS	least-squares
MADRS	Montgomery-Åsberg Depression Rating Scale
MAR	missing at random
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures

Abbreviation	Definition
PK	Pharmacokinetic
PT	preferred term
QD	once daily
RAS	randomized analysis set
REML	restricted maximum likelihood
SAP	statistical analyses plan
SAF	safety analysis set
SD	standard deviation
SDS	Sheehan Disability Scale
SE	standard error
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TRD	treatment-resistant depression
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This document is the statistical analysis plan (SAP) for the Denovo Biopharma LLC (Denovo) study DB104-01 titled "A Biomarker-Guided, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Liafensine in Patients with Treatment-Resistant Depression." It is prepared based on Protocol Amendment 2 dated 29 Aug 2022 and Case Report Form (CRF) 1.0 dated 23 Mar 2023.

Populations for analysis, data handling rules, and statistical methods are described within this document. The statistical analyses and summary tabulations described in this document, including safety, tolerability, efficacy, and pharmacokinetics (PK), will provide the basis for the results sections of the clinical study report for this trial.

The statistical analysis for the study will be performed by NJS Associates, a Denovo-designated contract research organization.

1.1. Objectives

1.1.1. Primary Objective

The primary efficacy objective is to demonstrate that liafensine is superior to placebo in Denovo Genomic Marker 4 (DGM4)-positive patients with treatment-resistant depression (TRD) as assessed by the change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to Day 42 of double-blind treatment.

1.1.2. Secondary Objectives

The key secondary efficacy objective is to evaluate the change from baseline to Day 42 in DGM4-positive patients with TRD treated with liafensine vs placebo on the Clinical Global Impressions Scale-Severity (CGI-S).

Safety Objectives:

- To compare the safety and tolerability of liafensine vs placebo in all randomized patients with TRD who received at least one dose of study drug during double-blind treatment
- To evaluate safety for liafensine 1 mg once daily (QD) and 2 mg QD vs placebo in both DGM4-positive and DGM4-negative patients

Other Secondary Efficacy Objectives:

- To evaluate Clinical Global Impressions Scale-Improvement (CGI-I) at Day 42 in DGM4-positive patients with TRD treated with liafensine vs placebo
- To evaluate the change from baseline to Day 42 in DGM4-positive patients with TRD treated with liafensine vs placebo on the patient-reported functionality with Sheehan Disability Scale (SDS)

1.1.3. Exploratory Objectives

- To compare the proportion of DGM4-positive patients with TRD who respond to liafensine after 6 weeks of treatment vs placebo (response is defined as ≥ 50% improvement from baseline in MADRS total score at Day 42)

- To compare the proportion of DGM4-positive patients with TRD who are in remission after 6 weeks of treatment with liafensine vs placebo (remission is defined as MADRS total score ≤ 10 at Day 42)
- To evaluate the change from baseline to Day 42 in DGM4-positive patients with TRD treated with liafensine vs placebo on MADRS anhedonia subscale and individual items
- To compare the efficacy of liafensine vs placebo in DGM4-negative patients with TRD, as assessed by change in MADRS total score from baseline to Day 42
- To evaluate efficacy for liafensine 1 mg QD and 2 mg QD vs placebo in both DGM4-positive and DGM4-negative patients
- To evaluate the PK of liafensine as part of the population PK analyses

1.2. Endpoints

1.2.1. Primary Endpoint

- Change in MADRS total score from baseline to Day 42, in DGM4-positive patients

1.2.2. Secondary Endpoints

Key Efficacy Endpoint:

- Change in CGI-S from baseline to Day 42, in DGM4-positive patients

Safety Endpoints:

- Adverse events (AEs) as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy
- Laboratory abnormalities as characterized by type, frequency, severity, and timing
- Vital signs including supine (after at least 5-min rest) and standing (after 1-min and 3-min standing), blood pressure (BP) and heart rate (HR), weight, electrocardiogram (ECG), clinical laboratory evaluation, Discontinuation-Emergent Signs and Symptoms (DESS) scale, and Columbia-Suicide Severity Rating Scale (C-SSRS) data

Other Secondary Efficacy Endpoints:

- CGI-I at Day 42, in DGM4-positive patients
- Change in SDS from baseline to Day 42, in DGM4-positive patients

1.2.3. Exploratory Endpoints

- Treatment response (defined as ≥ 50% improvement from baseline in MADRS total score at Day 42) in DGM4-positive patients
- Remission (defined as MADRS total score ≤ 10 at Day 42) in DGM4-positive patients
- Change in MADRS anhedonia subscale and individual items from baseline to Day 42, in DGM4-positive patients
- Change in MADRS total score from baseline to Day 42, in DGM4-negative patients
- Change in MADRS total score from baseline to Day 42 in 1 mg QD group and 2 mg QD group, in both DGM4-positive and DGM4-negative patients

2. STUDY DESIGN

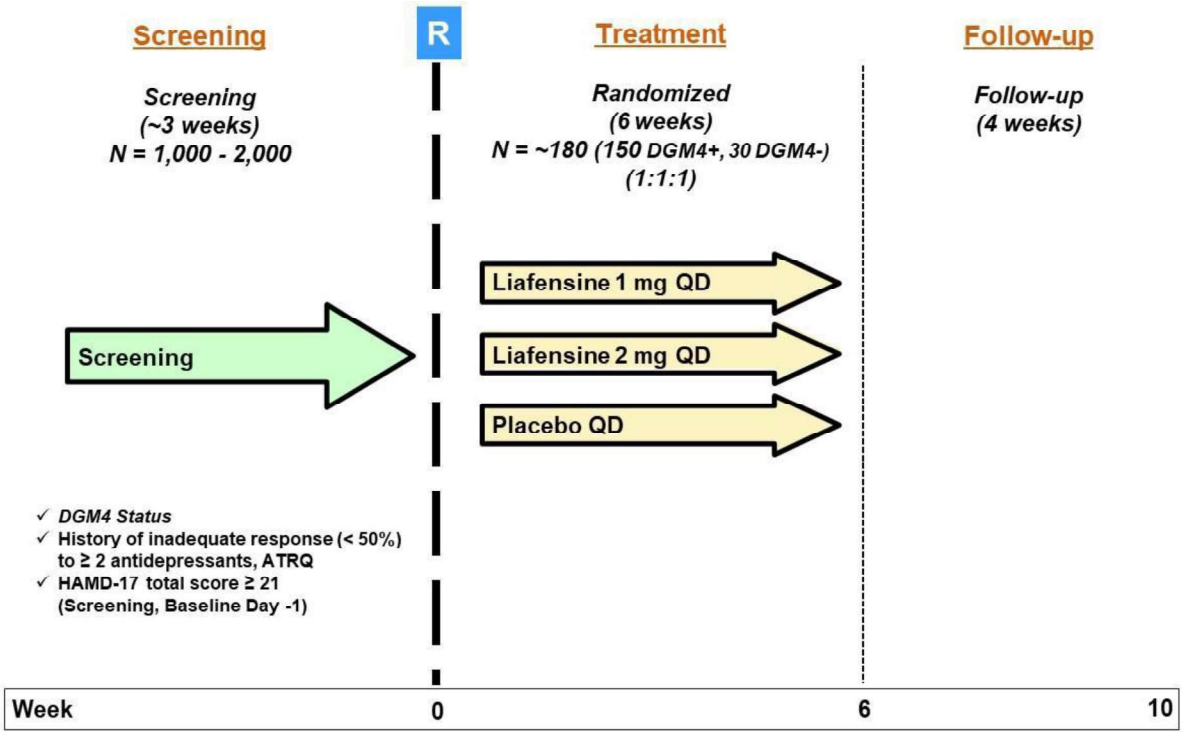
2.1. Design Overview

This study will be conducted as a multicenter, randomized, double-blind, placebo-controlled Phase 2b trial to assess the efficacy, safety, tolerability, and PK of liafensine. The study includes an up to 21-day screening period (the screening period may exceed 21 days if a prolonged washout is required).

Approximately 180 patients with TRD who meet all eligibility criteria will be randomized in a 1:1:1 ratio to receive either placebo QD, liafensine 1 mg QD, or liafensine 2 mg QD for 6 weeks. Approximately 150 randomized patients will be genotype GG for DGM4 (DGM4-positive) and approximately 30 randomized patients will be genotype AA or AG for DGM4 (DGM4-negative). DGM4 status (positive vs negative) of randomized patients will be blinded to the sites, patients, and sponsor. An interactive response technology (IRT) system will be used for blinding to DGM4 status, and to achieve the correct randomization ratio of DGM4-positive:DGM4-negative patients by randomly excluding most screened DGM4-negative patients (~80%). Randomization will be stratified by DGM4 status (positive vs negative) and region (North America vs Other). Patients who complete the study or discontinue after randomization will have 2 post-study follow-up visits (14 days after the last administered dose of study drug, and 28 days after the last administered dose of study drug); the 2nd follow-up visit will be conducted via phone call.

The overall study design is shown in Figure 1.

Figure 1. Study Design



Abbreviations: ATRQ = Antidepressant Treatment Response Questionnaire; DGM4 = Denovo Genomic Marker 4; HAMD-17 = Hamilton Depression Rating Scale - 17 Item; QD = once daily; R = randomization.

Patients will be randomly assigned through an IRT system in a 1:1:1 ratio to receive either placebo QD, liafensine 1 mg QD, or liafensine 2 mg QD for 6 weeks.

Randomization Phase:

Placebo QD

- Day 1 through Day 42: two placebo tablets QD

Liafensine 1 mg QD

- Day 1 through Day 42: one 1 mg liafensine tablet and one matching placebo tablet QD

Liafensine 2 mg QD

- Day 1 through Day 7: one 1 mg liafensine tablet and one matching placebo tablet QD
- Day 8 through Day 42: two 1 mg liafensine tablets QD

2.2. Schedule of Assessments

The schedule of assessments is found in Table 1 of the protocol. Study procedures and assessments are described in Section 7 of the protocol.

2.3. Sample Size Calculation

Eligible patients will be randomized 1:1:1 to receive placebo QD, liafensine 1 mg QD, or liafensine 2 mg QD. The primary analysis is to assess treatment difference in MADRS total score change from baseline (Visit 3, Day -1) to Visit 7 (Day 42), between the combined liafensine 1 mg QD and 2 mg QD doses vs placebo, in DGM4-positive patients. A sample size of 47 randomized DGM4-positive patients per arm is sufficient to detect a 4.5-unit difference between the combined liafensine 1 mg QD and 2 mg QD treatment groups and the placebo treatment group in the change in MADRS total score from baseline to Day 42 with 80% power at the 2-sided 0.05 alpha level, assuming a standard deviation (SD) of 9 units.

To compensate for potential loss of power due to randomized patients who do not take at least one dose of study drug or who do not have a post-randomization efficacy evaluation (~5%), a total of approximately 150 DGM4-positive patients (50 DGM4-positive patients per arm) will be randomized.

To examine trend in the total patient population and in the subgroup of DGM4-negative patients in order to evaluate DGM4 as a potential biomarker for predicting response to liafensine, approximately 20% additional DGM4-negative patients (10 per arm, total 30) will also be randomized. The sample size of 30 randomized patients in the DGM4-negative group is not estimated based on formal statistics in terms of power and alpha level.

Sample size re-estimation may be conducted if the percentage of missing data at Day 42 visit is higher than expected and/or if the observed variance is higher than the one assumed in the sample size estimation.

2.4. Timing of Analysis

2.4.1. Interim Analysis

No interim analysis will be performed.

2.4.2. Final Analysis

The final analysis for the clinical study report will be performed after the database has been locked and study has been unblinded.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. General Methods

Statistical analysis will be performed using SAS® software Version 9.4 or later (SAS 2001).

For continuous variables, descriptive statistics will include the number of subjects (n), mean, SD, median, minimum, and maximum. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects including missing data, ie, will add up to 100%.

The estimated mean and median for a set of values should be calculated to one more decimal place than the raw (observed) data and rounded appropriately. Standard errors (SE) (or SD) should be calculated to two decimal places beyond the raw (observed) data and rounded appropriately. The decimal place for minimum and maximum should be the same as raw (observed) data. Percentage values should be reported with one digit to the right of the decimal point. When numerator value is "0," it should be displayed as "0." Further, a maximum of two decimal places will be used for all summary statistics unless otherwise specified.

Summaries presented by visit will be based on the scheduled assessments as planned in the protocol. Unscheduled assessments will not be included in the by-visit summary tables, however, will be included in the listings. Any unscheduled visit that falls within a visit window period without a scheduled visit will be used in summary tables. The summary tables and listings will be presented by DGM4 status (positive/negative) where noted, treatment group, and overall. The treatment groups are defined as:

- Placebo QD
- Liafensine 1 mg QD
- Liafensine 2 mg QD
- Liafensine 1 mg and 2 mg QD

3.2. Definition of Baseline

Baseline value is defined as the last available value collected before the first dose date of study drug for all safety laboratory, safety ECG, vital sign, and efficacy values.

3.3. Study Day

Study Day is relative to the start date of liafensine or placebo treatment:

- If analysis date is on or after the liafensine or placebo treatment start date,
  Study Day = analysis date – treatment start date + 1.
- If analysis date is before the liafensine or placebo treatment start date,
  Study Day = analysis date – treatment start date.

3.4. Study Visits

Study visits in the electronic data capture (EDC) datasets include Screening 1 (Visit 1) and Screening 2 (Visit 2), Day -1 (Visit 3), Day 7 (Visit 4), Day 14 (Visit 5), Day 28 (Visit 6), Day 42 (Visit 7/End of Treatment [EOT]), Day 14 and Day 28 post-last dose follow-up, and any

unscheduled visits. Study visits will be windowed so that data recorded at any time have the potential to be included in summaries. The following visit window conventions will be followed:

Visit	Visit Number	Day	Window
Screening 1	1		
Screening 2	2		
Visit 3	3	-1	-1 to 3
Visit 4	4	7	4–10
Visit 5	5	14	11–20
Visit 6	6	28	21–34
Visit 7/EOT	7	42	35–49

Unscheduled visits will not be used in the summary by visit unless otherwise specified, the unscheduled visit values will be considered in the summary of worst change from baseline.

3.5. Coding Dictionaries

Medical history, medical or surgical procedures, and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 or higher.

Prior and concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary March 2022.

Adverse events and laboratory values will be classified as mild, moderate, or severe.

3.6. Stratified Analysis

Efficacy analyses will be stratified by biomarker status and region. Details are presented under the analysis for each endpoint.

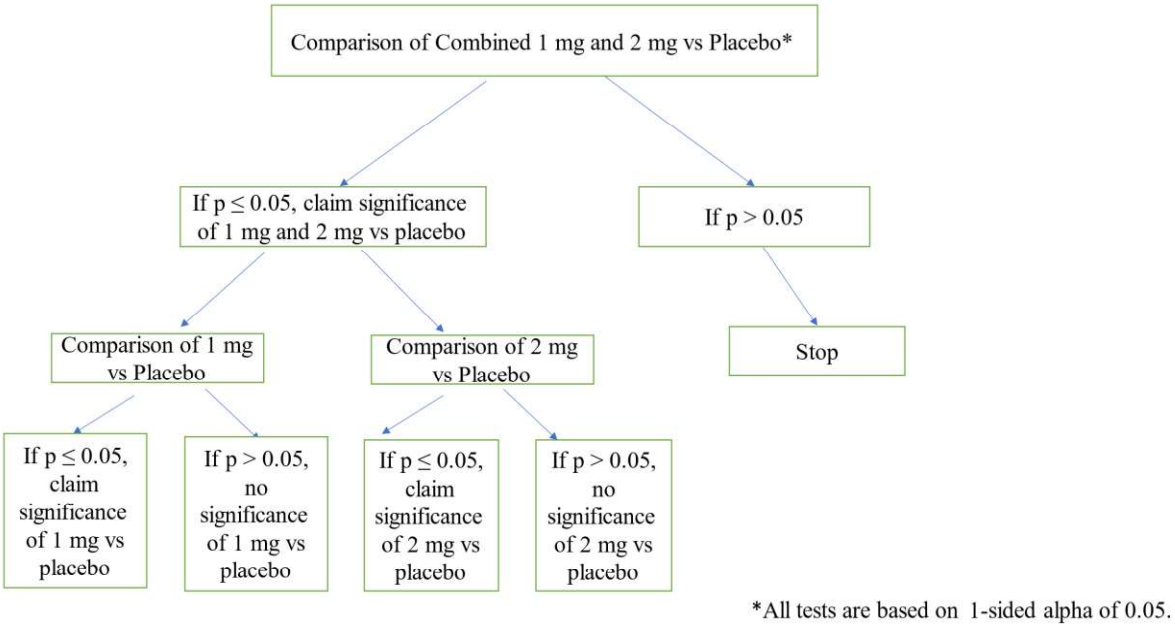
3.7. Testing Hypotheses and Multiple Comparisons

All statistical tests for the treatment comparison of efficacy endpoints will be based on a 1-sided alpha level of 0.05. For each endpoint, the null hypothesis is that the effects of each of the two liafensine treatment arms and placebo are the same. The alternative hypothesis is that liafensine is better than placebo.

As illustrated in Figure 2, the family-wise Type I error rate will be controlled at a fixed 1-sided alpha level of 0.05 using a closed testing procedure for multiple dose comparisons and multiple endpoint comparisons in DGM4-positive patients (Marcus 1976). In the closed testing procedure, the average effect of liafensine 1 mg and 2 mg dose groups will be first compared with the placebo group on change in MADRS total score from baseline to Day 42 in DGM4-positive patients. If the 1-sided p-value was ≤ 0.05, then the 1-sided p-values are calculated for the comparisons of 1 mg dose vs placebo and 2 mg dose vs placebo, respectively. If both individual p-values are ≤ 0.05, a significant treatment effect is declared for both dose groups. If only one p-value is ≤ 0.05, a significant treatment effect is declared for the corresponding dose group. All

other efficacy endpoints will not be controlled for multiplicity with nominal p-values provided for the exploratory purpose only.

Figure 2. Statistical Testing Procedure



3.8. Assessments

3.8.1. Montgomery-Åsberg Depression Rating Scale

Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item clinician-administered scale, designed to be particularly sensitive to antidepressant treatment effects in patients with major depression (Montgomery 1979). Each MADRS item is rated on a 0 to 6 scale. The MADRS total score is calculated as the sum of the 10 individual item scores; the total score can range from 0 to 60. Higher MADRS scores indicate higher levels of depressive symptoms.

3.8.2. Clinical Global Impressions Scale-Severity

Clinical Global Impressions Scale-Severity (CGI-S) asks the clinician one question: "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" which is rated on the following seven-point scale: 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients (Guy 1976).

This rating is based upon observed and reported symptoms, behavior, and function in the past seven days. Clearly, symptoms and behavior can fluctuate over a week; the score should reflect the average severity level across the seven days.

3.8.3. Clinical Global Impressions Scale-Improvement

Clinical Global Impressions Scale-Improvement (CGI-I) is similarly simple in its format (Guy 1976). Each time the patient is seen after medication has been initiated, the clinician compares the patient's overall clinical condition to the one-week period just prior to the initiation of medication use (the so-called baseline visit). The CGI-S score obtained at the baseline (initiation) visit serves as a good basis for making this assessment. Again, only the following one query is rated on a seven-point scale: "Compared to the patient's condition at admission to the project (prior to medication initiation), this patient's condition is: 1 = very much improved since the initiation of treatment; 2 = much improved; 3 = minimally improved; 4 = no change from baseline (the initiation of treatment); 5 = minimally worse; 6 = much worse; 7 = very much worse since the initiation of treatment."

The CGI-I score generally tracks with the CGI-S such that improvement in one follows the other. Anchors for scoring, however, are quite different, and the CGI-I is based upon changes from the initiation of treatment in contrast to changes from the preceding week of treatment. Consequently, the two CGI scores can occasionally be dissociated such that a clinician may notice changes in the CGI-I relative to baseline despite no recent changes in the overall CGI-S score or vice versa.

3.8.4. Sheehan Disability Scale

Sheehan Disability Scale (SDS) is used to assess functional impairment in three major life domains: work, social life/leisure activities, and family life/home responsibilities (Sheehan 2008). It is a five-item scale that will be completed by the participant. Three items use a Likert scale with a 10-point range (0 / Moderately to 10 / Extremely) and two items are open-ended (eg, "On how many days in the last week did you…?").

The first three items assess disruption of (1) work (2) social life/leisure activities, and (3) family life/home responsibilities using a 0-10 rating scale. The scores for the first three items are summed to create a total score of 0-30 where a higher score indicates greater impairment. It also has one item on days lost from school or work and one item on days when underproductive.

3.8.5. Columbia-Suicide Severity Rating Scale

Columbia-Suicide Severity Rating Scale (C-SSRS) was designed to quantify the severity of suicidal ideation and behavior (Posner 2011). C-SSRS is a measure used to identify and assess individuals at risk for suicide. Questions are phrased for use in an interview format but can be completed as a self-report measure if necessary. C-SSRS measures four constructs: the severity of ideation, the intensity of ideation, behavior, and lethality. It includes "stem questions," which if endorsed, prompt additional follow-up questions to obtain more information. There are four versions of the scale available, including: 1) Baseline/screening version, which allows practitioners to gather a lifetime and recent 12 months history of suicidal ideation and/or behavior; 2) Since Last Visit version for assessment of suicidal thoughts and behaviors since C-SSRS was last administered; 3) Screen version, a shortened version of the full form (3-6 questions) most commonly used in clinical triage settings; 4) Risk Assessment Page, which provides a checklist of protective and risk factors of suicidality.

3.8.6. Discontinuation-Emergent Signs and Symptoms Scale

Discontinuation-Emergent Signs and Symptoms Scale (DESS) is used to monitor patients for discontinuation symptoms (Rosenbaum 1998). It includes 43 signs or symptoms for which the patient indicates whether there has been any change since their last visit – indicating new symptom, old symptom but worse, old symptom but improved, old symptom but unchanged, symptom not present. The DESS total score on a given day is calculated as the count of items with new symptoms or old symptoms but worse over all 43 items. For missing items, it will be imputed as the average from the non-missing items. The total score can range from 0 to 43. The number and proportion of subjects with the sum of zero, 1, 2, 3, and ≥ 4 will be presented each day and by the treatment arm. Treatment comparison will be performed each day from Day 1 to Day 14 using the Cochran-Mantel-Haenszel (CMH) test stratified by region and biomarker status. The average DESS total score over the assessment period will be calculated for each subject and compared between treatment group using the Wilcoxon rank-sum test.

3.9. Handling of Missing Data

3.9.1. Handling of Partial Dates for Adverse Events

When determining the treatment-emergent adverse events (TEAEs), partial adverse event start and/or end dates will be handled as shown in Table 1.

Table 1. Imputation Rules for Adverse Event Partial Dates

Date	Missing Part	Imputation Rule
Start Date	Missing Day	Assign the first day of month unless it is the same month and year of the first dose of study treatment. Otherwise, assign date of first dose of study treatment or adverse event end date (if not missing), whichever is earlier.
	Missing Day, Month	Assign Jan 01 unless the year is year of first dose of study treatment. Otherwise, assign date of first dose of study treatment or AE end date (if not missing), whichever is earlier.
	Missing Day, Month, Year	Assign the date of first dose of study treatment or AE end date (if not missing), whichever is earlier.
End Date	Missing Day	Assign the last date of the month or death date or data cutoff date (or end of study date), whichever is earliest.
	Missing Day, Month	Assign Dec 31 or death date or data cutoff date (or end of study date), whichever is earliest.
	Missing Day, Month, Year	If ongoing, the end date is missing. Otherwise, assign death date or data cutoff date (or end of study date), whichever is earlier.

3.9.2. Handling of Partial Dates for Medications

When determining if a medication is a prior or concomitant medication, partial start and/or end dates will be handled as shown in Table 2.

Table 2. Imputation Rules for Medication Partial Dates

Date	Missing Part	Imputation Rule
Start Date	Missing Day	Assign the first day of month unless it is the same month and year of the first dose of study treatment. Otherwise, assign date of first dose of study treatment or medication end date (if not missing), whichever is earlier.
	Missing Day, Month	Assign Jan 01 unless the year is year of first dose of study treatment. Otherwise, assign date of first dose of study treatment or medication end date (if not missing), whichever is earlier.
	Missing Day, Month, Year	Assign date of first dose of study treatment or medication end date (if not missing), whichever is earlier.
End Date	Missing Day	Assign the last date of the month or death date or data cutoff date (or end of study date), whichever is earliest.
	Missing Day, Month	Assign Dec 31 or death date or data cutoff date (or end of study date), whichever is earliest.
	Missing Day, Month, Year	If ongoing, the end date is missing. Otherwise, assign death date or data cutoff date (or end of study date), whichever is earlier.

The imputed date will be used to categorize TEAE, prior/concomitant medication. The data listings will report original data instead as the imputed date.

3.9.3. Handling of Missing Data for MADRS

For MADRS, the total score is set to missing for any patient if 50% or more items are missing at an assessment. If less than 50% of items are missing, the missing items will take the average from the non-missing items. These calculated total scores will not be rounded to whole numbers.

Missing data for the total score of MADRS will be maintained as missing unless specified otherwise.

3.9.4. Handling of Missing Data for Other Efficacy Scales

Missing data for other efficacy scales will be maintained as missing unless specified otherwise.

4. ANALYSIS SETS

4.1. Randomized Analysis Set

The randomized analysis set (RAS) includes all randomized patients in this study. This analysis set will be used for a sensitivity analysis of the primary and key secondary efficacy endpoints for DGM4-positive patients. The RAS population will be analyzed by treatment randomization regardless of the actual treatment received.

4.2. Full Analysis Set

The full analysis set (FAS) includes all randomized patients who took at least one dose of study drug and had a post-randomization efficacy evaluation. The FAS population will be analyzed by treatment randomization regardless of the actual treatment received. The primary and secondary efficacy results of the study will be based on analysis in FAS patients who are DGM4 positive.

4.3. Safety Analysis Set

The safety analysis set (SAF) includes all patients who took at least one dose of study drug. The safety population will be analyzed by the actual treatment received regardless of treatment randomized.

4.4. Per Protocol Analysis Set

The per protocol analysis set (PP) excludes all patients with one of the following violations:

- Violation of major inclusion or exclusion criteria as determined by the sponsor prior to the database lock
- Study treatment compliance at < 80% or > 120%
- Had disallowed medications during > 50% of the treatment period
- Were mis-randomized
- Others which may impact reliable interpretation of the outcome

All patients with the violations above will be reviewed as potential important protocol deviations. The final list of per protocol deviations will be reviewed and finalized on individual cases prior to the database lock and unblinding. Additional information on protocol deviations is provided in Section 5.1.2.

5. STATISTICAL METHODOLOGY

5.1. Population Characteristics

5.1.1. Study Subjects Disposition

The number of subjects in the FAS and SAF will be presented. The percentage of subjects in FAS will be calculated using the number of subjects in the SAF as denominator.

- Number screened
- Number of screen failures: due to DGM4 status vs all other reasons
- Number randomized
- Number and percentage of subjects who had at least one dose of study treatment
- Number and percentage of subjects who completed or discontinued treatment, primary reason for discontinuation of treatment assigned to one of the reasons listed below
  - Adverse Event
  - Pregnancy
  - Study Terminated by Sponsor
  - Death
  - Withdrawal of Consent to Treatment
  - Other
- Number and percentage of subjects who completed or discontinued the study, primary reason for study discontinuation assigned to one of the reasons listed below
  - Completed Protocol
  - Adverse Event
  - Withdrawal of Consent to Study
  - Death
  - Lost To Follow-Up
  - Study Terminated by Sponsor
  - Other

Subjects disposition data will also be presented in data listings.

5.1.2. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the clinical protocol.

Protocol deviations will be classified by the sponsor or designee prior to the final analysis and important protocol deviations will be identified as those deviations from the study protocol that may significantly impact the completeness, accuracy, and/or reliability of the trial data; that may significantly affect a subject's rights, safety, or well-being [ICH E3(R1) Q&As, 2013]. The number and percentage of subjects with an important protocol deviation will be tabulated for the SAF.

Separate listings for protocol deviations will also be presented.

5.1.3. Demography and Baseline Characteristics

Descriptive statistics, including number of subjects (n), mean, SD, median, minimum, and maximum, will be used to summarize the following parameters:

- Age (years)
- Weight (kg) at Baseline
- Height (cm) at Baseline
- Body Mass Index (kg/m^2) at Baseline

The following demographic categories will be summarized with the number and percentage of subjects:

- Age Groups (years): 18 to < 35, ≥ 35 to < 55, and ≥ 55; < 65 and ≥ 65
- Gender: Male, Female
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Other. The details of Other race will be listed as appropriate.
- Baseline scores of MADRS, CGI-S, and HAMD-17
- Number of years having major depressive disorder (MDD) or TRD
- Prior treatment classes, including antidepressant only, combination of antidepressant with others, and non-antidepressant medication which is used to support treatment of depression.

5.1.4. Medical History

System organ class (SOC) and preferred term (PT) of medical history will be coded with MedDRA Version 25.0 or higher. A subject will be counted only once within one SOC and one PT if the subject reported the same SOC and PT multiple times. The summary will be sorted by the frequency of SOCs and PTs in overall total.

Medical history information collected on "Medical History" CRF page will be listed in subject data listing.

5.1.5. Prior and Concomitant Medications

All medications will be coded using WHO Drug Dictionary March 2022.

A medication can be classified as either prior or concomitant medication. Prior medication is defined as any medication taken prior to the date of the first study treatment dose. Concomitant medication is defined as any medication taken on or after the date of the first study treatment dose through the end of study.

Prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Classification (2^{nd} level, chemical subgroup [ATC-2]) and preferred name. A subject will only be counted once within each ATC-2 code and within each preferred name. ATC-2 and preferred name will be sorted in descending frequency for the overall number of subjects and then alphabetically for ties.

Prior and concomitant medications will also be presented in data listings.

5.2. Concomitant Procedures

All procedures will be coded using MedDRA Version 25.0 or higher.

Concomitant procedures will also be presented in data listings.

5.3. Exposure of Study Treatment

Exposure for study medications will be summarized separately using SAF by treatment group.

The exposure summary will present descriptive statistics for the following:

- Number of tablets taken
- Number of tablets missed
- Treatment duration (days) = date of last dose – date of first dose + 1
- Actual dose = sum of actual tablets administered
- Number of subjects with at least one dose adjustment with a breakdown of reasons for dose adjustment

Overall compliance during the treatment period is calculated as:

% of compliance = (# of tablets taken / # of tablets expected during the treatment period) * 100

By visit summary of compliance will be presented.

All study treatment administration data will be presented in data listings.

5.4. Efficacy Analysis

All analyses will be presented for DGM4-positive, DGM4-negative, and both DGM4-positive and DGM4-negative subjects.

The analyses of the primary and key secondary efficacy endpoints will be conducted on the FAS. Supportive sensitivity analyses will be performed in the per protocol analysis set for primary and key secondary efficacy endpoints unless otherwise specified.

5.4.1. Primary Endpoint: Change in MADRS Total Score from Baseline to Day 42, in DGM4-Positive Patients

5.4.1.1. Estimand

The following components are considered in the construction of the estimand, the main clinical quantity of interest to be estimated in the study:

- Objective: To demonstrate that liafensine (1 mg QD or 2 mg QD) is superior to placebo in DGM4-positive patients with TRD as assessed by the change in MADRS total score from baseline to Day 42 of double-blind treatment
- Intercurrent events (ICEs): Early termination of treatment due to various reasons or starting a prohibited medication. A detailed list of ICEs is provided at the end of this section.
- Question of interest: For a patient with TRD for whom a short-term monotherapy would be indicated, what would be the expected effect of liafensine on severity of depressive

episodes at Week 6, if taken as directed for 6 weeks without initiating prohibited medications as defined in Protocol Section 5.3?

The primary estimand is defined with the following components per ICH E9(R1):

- The treatment condition of interest: TRD patients who meet all eligibility criteria will be randomized in a 1:1:1 ratio to receive either placebo QD, liafensine 1 mg QD, or liafensine 2 mg QD for 6 weeks.
- Population: patients with TRD with the DGM4-positive biomarker
- Endpoint at subject level: change in MADRS total score from baseline (Visit 3, Day -1) to Day 42 (Visit 7)
- Population-level summary: For each treatment arm, the least-square (LS) mean of the primary endpoint will be calculated in each arm using the method described in Section 5.4.1.2. Treatment comparisons will be based on the LS means.

Intercurrent events and corresponding strategies:

Intercurrent events to be considered for this analysis are those events that cause the MADRS at Day 42 to be either missing or compromised. The primary method will be mixed model for repeated measures (MMRM) with imputation assuming missing at random (MAR), ie, a hypothetical strategy per ICH E9(R1). Hence, missing values will be imputed with non-missing values in the same treatment group. A fully conditional specification (FCS) method with predictive mean matching approach will be used in the imputation of missing MADRS score change from baseline as continuous variables (Buuren 2007). The following sensitivity analyses will be performed, with details described in Section 5.4.1.3:

- A tipping-point analysis for the primary analysis result
- MMRM without imputation
- MMRM with multiple imputation using a patter-mixture model, as well as a tipping point analysis for this imputation method
- Sensitivity analyses based on RAS

MMRM will be implemented using SAS Mixed procedure with the default REML (restricted maximum likelihood) estimation.

ICEs in this study are listed below:

- Treatment discontinuation due to AE
- Withdrawal of consent to treatment discontinuation
- Other/Lost to follow-up
- Use of prohibited medications
- Pregnancy
- Death

5.4.1.2. Main Estimator

The primary efficacy analysis will be performed in DGM4-positive patients at 1-sided significance level of 0.05 using MMRM with imputation based on the MAR assumption. The model will include the fixed effects of treatment, visit (categorical covariate), treatment-by visit interaction, treatment by baseline MADRS total score, baseline MADRS total score (continuous covariate), and region. Change from baseline in weekly visits at Days 7, 14, 28, and 42 will be

the repeated outcome measures, and the model will use an unstructured variance-covariance matrix. If the model does not converge the algorithm (Lu 2010) will be used to assist in the convergence.

The following hypothesis will be tested based on the test statistics from the mixed model:

H_0: $u_i - u_0 = 0$ vs. H_A: $u_i - u_0 \neq 0$

where u_i is the expected mean change from baseline in MADRS for liafensine at Day 42 and u_0 is the expected mean change from baseline in MADRS for placebo at Day 42. In H_0 and H_A above, i = 1, 2, 3 are for liafensine 1 mg, 2 mg, and both arms pooled, respectively, for implementing the closed testing procedure described in Section 3.7. The LSMESTIMATE statement in SAS Mixed procedure will be used to test the global null hypothesis of no treatment difference between both active arms and placebo while keeping all 3 treatment groups separately. Please see sample SAS code in Appendix 8.2.

The LS mean for change from baseline in MADRS total score at Day 42 for the combined liafensine treatment arms (1 mg QD and 2 mg QD) and placebo arm will be estimated from the MMRM model. The comparison of the change in MADRS total score from baseline to Day 42 between each of the two liafensine treatment arms and placebo will be carried out using the same approach. Separate figures with the mean change (± SD) and LS mean change (± SE) by visit will be displayed.

In the analysis, data collected after initiation of prohibited medications will be used unless otherwise specified. All available data collected from all subjects before or after ICEs will be included in the analysis unless otherwise specified. Missing data due to any ICEs will be imputed using SAS MI procedure with the FCS statement and REGPMM option to implement the fully conditional specification method with predictive mean matching approach described in Section 5.4.1.1. For MADRS, the total score is set to missing if 50% or more items are missing at an assessment. When this occurs, the change from baseline value will be imputed without using any of the non-missing items.

The following variables will be included in the imputation model: region, baseline MADRS score, and change from baseline at Weeks 1, 2, 4, and 6. One hundred fully imputed datasets will be created. The MMRM described above will be used for treatment comparisons. Treatment effects (difference in LS means between treatment arms) from these 100 analyses will be combined to generate final results using Rubin's method implemented by SAS MIANALYZE procedure.

The following tables and figures will be generated to assess the MAR assumption:

1. A by-visit and overall summary table for (n, %), and cumulative (n, %) for reasons of missing value or early dropout in each arm due to:
   - AE including death
   - Withdrawal of consent to treatment discontinuation
   - Other reasons
   - Total (All of the above)

   Within each arm, the summary statistics of the primary endpoint will also be generated by dropout reason at each visit. This table will also be used to support the figure below.

2. For each arm, generate a line graph for mean change from baseline (y-axis) over time (x-axis) by dropout reasons. There will be 4 lines on this figure to represent each dropout reasons:

   - None (completers)
   - Dropout due to AE including death
   - Dropout due to withdrawal of consent to treatment discontinuation
   - Dropout due to other reasons

   In addition, a figure similar to the one above will be generated, with mean change from baseline replaced with a line graph for each subject. Subjects with the same reason for dropout will have the same color.

5.4.1.3. Sensitivity Estimator

Four types of sensitivity analyses will be conducted on the primary endpoint.

1. A tipping point analysis to assess the robustness of the primary analysis results. The imputed missing values will be decreased or increased gradually, and treatment comparisons will be repeated. If the original result is significant and a large shift from the original imputed values needs to be done to reverse significance, the result is considered robust. The steps below will be followed.

   If the primary analysis result is significant:

   1) Increase each imputed value in the active arms by 1 and repeat the primary analysis using MMRM. If the treatment effect is still significant, each imputed value in the active arms will be further increased by 1 until the result is non-significant.
   2) Repeat the tipping point analysis above but decrease each imputed value in the placebo arm by 1 until the result is non-significant.
   3) Repeat the tipping point analysis by increasing each imputed value in the active arms by 1 and decreasing each imputed value in the placebo arm by 1 until the result is non-significant.

   If the primary analysis result is non-significant:

   1) Decrease each imputed value in the active arms by 1 and repeat the primary analysis using MMRM. If the treatment effect is still non-significant, each imputed value in the active arms will be further decreased by 1 until the result is significant.
   2) Repeat the tipping point analysis above but increase each imputed value in the placebo arm by 1 until the result is significant.
   3) Repeat the tipping point analysis by decreasing each imputed value in the active arms by 1 and increasing each imputed value in the placebo arm by 1 until the result is significant.

   There are two active dose groups in this study. In the description above, significance or non-significance refers to the result after multiplicity adjustment, and shift from the imputed value only involves the active and placebo arms under tipping point analysis. The imputed values of the other active dose group will remain the same in the pooled analysis. A shift parameter will be applied to each dose arm separately in the pooled analysis. After each tipping point analyses is completed, up to 3 results before reaching

the tipping point, as well as the result that reverses statistical significance or non-significance will be reported.

2. MMRM without imputation

   The same model in the primary analysis will be used without imputation using the treatment policy strategy per ICH E9(R1) (Polverejan 2023). This analysis will be used to assess the impact of imputing missing values based on the MAR assumption.

3. MMRM with imputation using pattern mixture model

   This sensitivity estimator will be using a control-based multiple imputation method (Ratitch 2013). This sensitivity analysis does not rely on the MAR assumption. Data collected after initiation of prohibited medications will not be used unless otherwise specified. Missing data due to all ICEs will be handled per specifications below unless otherwise specified.

   In this sensitivity analysis, imputation will be implemented using SAS MI procedure with FCS statement and REGPMM option, as well as MNAR statement with MODELOBS option to identify observations from the placebo arm for deriving the imputation models, ie, assuming all missing data will have a profile that equals the profile of the placebo arm for all time points. The variables to be used in the imputation are region, baseline values, and change from baseline values observed at Weeks 1, 2, 4, and 6.

   One hundred fully imputed datasets will be created. The MMRM described in Section 5.4.1.2 will be used for treatment comparisons. Treatment effects (difference in LS means between treatment arms) from these 100 analyses will be combined to generate the final results using Rubin's method with SAS MIANALYZE procedure.

   A tipping point analysis for this sensitivity analysis will also be conducted to assess the robustness of the result. The same steps described in the first sensitivity analysis will be followed.

4. Sensitivity Analyses based on RAS

   A set of sensitivity analyses listed below will be performed using DGM4-positive patients in RAS. The same MMRM in the primary and sensitivity analyses described above will be carried out with the exclusion of the following fixed effect: treatment by baseline MADRS total score. In other words, the model will include the fixed effects of treatment, visit (categorical covariate), treatment by visit interaction, baseline MADRS total score (continuous covariate), and region.

   The following analyses will be performed in this set of sensitivity analyses:

   1) The primary analysis, as well as the 1st and 2nd sensitivity analyses based on FAS will be repeated using RAS.
   2) For the 3rd sensitivity described above, ie, MMRM with imputation using pattern mixture model, the imputation will be based on intercurrent events described below.

   All randomized participants who discontinued early with missing data will be classified as Group 1, Group 2, and Group 3 based on the following rules:

- Group 1: Treatment discontinuation due to AE
- Group 2: Withdrawal of consent to treatment discontinuation; Other/Lost to follow-up; and Pregnancy
- Group 3: One death was observed in this study with unknown reason and undetermined relationship to the study drug

For subjects who were on prohibited medications, a hypothetical strategy will be applied. It is plausible that these prohibited medications may have additional efficacy effect on top of the study medication. To eliminate the assumed additional effect, data after the initiation of prohibited medication will be imputed with non-missing data in the same arm while the subject is on study medication. If the subject terminates the study medication early after initiation of prohibited medication, the missing data after treatment termination will be imputed according to the cause of termination stated in Groups 1-3 above.

Multiple imputations will be implemented using the SAS MI procedure with FCS statement and REGPMM option, as well as MNAR statement with MODELOBS option.

a) For missing values caused by treatment discontinuation due to AE from Group 1, missing values will be imputed using non-missing values in the placebo group.
b) For missing values due to Withdrawal of consent to treatment, Other/Lost to follow-up, or Pregnancy from Group 2, missing values will be imputed using non-missing value within the same treatment group.
c) From Group 3: One death with unknown reason and undetermined relationship to study drug occurred in this study. Missing data prior to death will be imputed based on the worst score from this subject, and data after death will not be imputed. Multiple imputations will be carried out using a normal random variable with mean equal to the worst score in the schedule visits of this subject, and variance equal to the observed variance from the same treatment arm at the same visit.
d) For subjects who used prohibited medications, data after initiation of prohibited medication will be imputed with non-missing data in the same arm while the subject is on study medication, same as b) above. If the subject terminates study medication early after initiation of prohibited medication, missing data after treatment termination will be imputed according to the cause of termination stated in Groups 1 to 3 above. See Appendix 8.6 for the implementation of multiple imputations.

5.4.2. Key Secondary Endpoint: Change in CGI-S from Baseline to Day 42, in DGM4-Positive Patients

The change in CGI-S from baseline (Visit 3, Day -1) to Day 42 (Visit 7) will be analyzed using the MMRM model without imputation similar to the one used in sensitivity analysis (2) for the primary efficacy endpoint described in Section 5.4.1.3. Separate figures with the mean change (± SD) and LS mean change (± SE) by visit will be displayed.

5.4.3. Other Secondary Endpoint: CGI-I at Day 42, in DGM4-Positive Patients

CGI-I at Day 42 (Visit 7) will be analyzed using the CMH test stratified by region. Summary statistics will be provided on the proportion of subjects in each category. Summary statistics on CGI-I as a continuous variable will also be provided including the mean and median.

5.4.4. Other Secondary Endpoint: Change in SDS from Baseline to Day 42, in DGM4-Positive Patients

The change in SDS from baseline (Visit 3, Day -1) to Day 42 (Visit 7) will be analyzed using the MMRM model without imputation similar to the one used in sensitivity analysis (2) for the primary efficacy endpoint described in Section 5.4.1.3.

5.4.5. Subgroup Analyses

Subgroup analyses for the primary endpoint will be considered for gender, ethnicity, and region, and may be explored for other factors (such as duration of MDD baseline severity in term of MADRS total score). Summary statistics will be provided for efficacy measures by treatment for each subgroup.

5.5. Safety Analysis

5.5.1. Adverse Events

Adverse events will be coded using MedDRA Version 25.0 or higher.

A TEAE is any AE that starts on or after the first day of study treatment or that worsens on or after the first day of study treatment, and within 30 days of the last administration of study treatment.

For the purpose of regulatory reporting, relationships of “Related” or “Unrelated” will be assessed and presented. Related to study drug suggests there is as at least a reasonable possibility that the drug caused the AE (ie, there is evidence or arguments to suggest a causal relationship between the drug and AE).

Unrelated to study drug will be assessed based on the following:

- Does not follow a reasonable temporal sequence from administration of drug
- Does not appear to worsen when the drug is re-administered
- There is not a reasonable possibility that the drug caused the AE
- An alternate etiology has been established, ie, the AE is more likely explained by another cause (eg, other study treatments or procedures, underlying medical conditions, concomitant medications, etc) than the study treatment

Missing relationships will not be imputed.

Potential liver injury, ie, suspected and/or confirmed Hy’s Law, and drug-induced liver injury (DILI) cases will be assessed as adverse events of special interest (AESIs) and must be reported as serious adverse events. Information of abnormal laboratory test results including the course and evolvement, clinical signs and symptoms, detailed medical history and concurrent medication, history and current lifestyle including alcoholic assumption, and history of exposure to environmental chemical agents will be used to assess the case(s).

An overall summary of TEAEs using frequencies and percentages of subjects will be presented based on the following categories:

- TEAEs
- Study drug related TEAE
- TEAE by worst severity
- Serious TEAE
- Study drug related serious TEAE
- TEAEs leading to study drug withdrawal
- TEAEs leading to study drug being on hold
- TEAEs leading to death
- AESIs

The following events will be tabulated by SOC and PT. SOC will be sorted by descending frequency and then alphabetically for tie. Within each SOC, PT will also be sorted by descending frequency and then alphabetically for ties, by the overall number of subjects. If a SOC or PT is reported more than once for a subject, the subject will only be counted once in the incidence for that SOC or PT.

- TEAEs
- Study drug related TEAE
- TEAE by worst severity
- Serious TEAE
- Study drug related serious TEAE
- TEAEs leading to study drug withdrawal
- TEAEs leading to study drug being on hold
- TEAEs leading to death
- AESIs

Summaries of events by decreasing frequency of PT include:

- TEAEs
- Study drug related TEAE
- Serious TEAE
- Study drug related serious TEAE

If a PT is reported more than once for a subject, the subject will only be counted once in the incidence for that PT.

The following listings will be provided:

- All AEs (flag TEAE)
- Serious Aes (flag TEAE)
- TEAEs leading to study drug withdrawal
- TEAEs leading to study drug being on hold
- TEAEs leading to death
- AESIs

5.5.2. Clinical Laboratory Evaluation

Blood chemistry, hematology, and urinalysis tests are listed in Table 3.

Table 3. Clinical Laboratory Tests

Blood Chemistry	Hematology	Urinalysis

• Alanine aminotransferase (ALT/SGPT)
• Alkaline phosphatase (ALP)
• Aspartate aminotransferase (AST/SGOT)
• Bilirubin (direct and total)
• Blood urea nitrogen (BUN)
• Calcium
• Chloride
• Cholesterol (total)
• Creatine kinase (CK)
• Creatinine
• Glucose (serum)
• Phosphorus
• Potassium
• Protein (albumin and total)
• Sodium
	• Hematocrit
	• Hemoglobin
	• MCH concentration (MCHC)
	• Mean corpuscular hemoglobin (MCH)
	• Mean corpuscular volume (MCV)
	• Platelet count
	• Red blood cell (RBC) count
	• White blood cell (WBC) differential
	  ○ Neutrophil count (absolute and %)
	  ○ Lymphocyte count (absolute and %)
	  ○ Monocyte count (absolute and %)
	  ○ Eosinophil count (absolute and %)
	• Basophil count (absolute and %)
	• WBC count
		• On-site macroscopic examination
		• Central lab microscopic examination (in the event of protein, blood, nitrite and/or leukocyte esterase noted in macroscopic)
		• Bilirubin
		• Blood (occult and cells)
		• Ketones
		• Leukocytes
		• Nitrite
		• pH
		• Protein
		• Specific gravity
		• Urobilinogen

Actual value, change from baseline, and percentage change from baseline for continuous parameters (analytes) of blood chemistry and hematology tests will be summarized by visit and treatment group using descriptive statistics (mean, median, SD, minimum, maximum, and number of subjects).

Baseline and post-baseline blood chemistry and hematology tests will be classified according to normal ranges as low, normal, and high. Shift of these tests from baseline to the maximum post-baseline values will be presented by treatment group using the number and percentage of subjects at each shift category. If applicable, some laboratory tests have two directions: hypo and hyper, where both directions will be presented in the shift table.

Liver function tests will be summarized by the following:

- Alkaline Phosphatase (ALP)
  - >1.5 × ULN
  - >2 × ULN
  - >3 × ULN
- Alanine Aminotransferase (ALT)
  - >3 × ULN
  - >5 × ULN
  - >10 × ULN

- Aspartate Aminotransferase (AST)
  - >3 × ULN
  - >5 × ULN
  - >10 × ULN
- Total Bilirubin (TBL)
  - >1.5 × ULN
  - >2 × ULN
  - >3 × ULN

ULN = upper limit of normal

The risk difference between treatment arms vs placebo, and 95% confidence interval will be calculated.

All laboratory values will be presented in data listings.

All other laboratory tests, including urinalysis, thyroid, pregnancy, and urine drug screen, will be presented in a data listing only.

5.5.3. Vital Signs

Vital signs will include measurement of blood pressure (BP) and heart rate (HR): supine (after at least 5-min rest) and standing (after1-min and 3-min standing).

Actual value of BP and HR, between supine and standing (after 1-min and 3-min standing) at each visit (timepoint if applicable) will be presented using descriptive statistics by treatment group. A figure with the mean (± SD) of vital sign parameters by visit will be displayed.

Number of subjects with changes in HR (> 20 and > 30) will be presented at baseline and each post-baseline visit. The risk difference between treatment arms vs placebo, and 95% confidence interval will be calculated.

A separate table with a decrease in systolic BP > 20 mmHg, or diastolic > 10 mmHg on standing from supine position will be presented at baseline and each post-baseline visit. The risk difference between treatment arms vs placebo, and 95% confidence interval will be calculated.

Percentage of patients with maximum systolic BP by category of BP post-baseline (< 90, ≥ 90, ≥ 120, ≥ 140, ≥ 160, and ≥ 180) will be presented.

Percentage of patients with maximum diastolic BP by category of BP post-baseline (< 60, > 60, > 90, > 110, and > 120) will be presented.

All vital signs data will be presented in a data listing.

5.5.4. DESS scale and C-SSRS data

Discontinuation-Emergent Signs and Symptoms scale and C-SSRS data will be summarized by descriptive statistics at each visit and by treatment group unless otherwise specified. Change from baseline at each visit will be presented using descriptive statistics by treatment group for C-SSRS. Please see Section 3.8.6 for details on DESS.

All DESS scale and C-SSRS data will be presented in a data listing.

5.5.5. 12-Lead Electrocardiograms

ECG parameters (Heart Rate, RR interval, QRS Duration, QT Interval, QTcF) will be assessed according to the schedule of assessments in Table 1 of the protocol.

12-lead ECG recordings will be performed in triplicate (at approximately 1-min intervals between each of the three recordings) at baseline, and single ECG for rest of visits.

QT corrected by Fridericia's formula is recommended: $QTcF = QT/RR^{0.33}$.

Actual value, change from baseline, and percent change from baseline at each visit (timepoint if applicable) will be presented using descriptive statistics by treatment group.

Shift of ECG overall interpretation from baseline to end of treatment visit will be prepared with number and percentage of subjects being reported with Normal, Abnormal, Abnormal Clinically Significant, and Not Done.

The QTcF interval will be summarized by the frequencies of subjects with absolute value and/or change from baseline using the criteria identified below:

- < 450
- ≥ 450 to < 480
- ≥ 480 to < 500
- ≥ 500
- <30 increases from baseline
- 30 to ≤ 60 increases from baseline
- > 60 increases from baseline

Subjects with abnormal ECG results, regardless of clinical significance, will be identified in data listings with flags for abnormalities.

5.5.6. Physical and Neurological Exam

Physical and Neurological exam data will be presented in a data listing.

5.6. Exploratory Analysis

5.6.1. Treatment Response in DGM4-Positive Patients

Treatment response is defined as ≥ 50% improvement from baseline in MADRS total score at Day 42 (Visit 7) in DGM4-positive patients. Response rate and corresponding 95% confidence interval for each treatment group will be derived by using Clopper-Pearson method (Clopper 1934). The comparison of response rate between treatment groups will be carried out using the CMH test. The percentage of subjects achieving response in MADRS by visit will be displayed in a bar chart.

5.6.2. Remission in DGM4-Positive Patients

Remission is defined as MADRS total score ≤ 10 at Day 42 (Visit 7) in DGM4-positive patients. Remission rate will be analyzed using the same methodology as described in Section 5.6.1. The percentage of subjects with remission by visit will be displayed in a bar chart.

5.6.3. Change in MADRS Anhedonia Subscale and Individual Items from Baseline to Day 42, in DGM4-Positive Patients

Change in MADRS anhedonia subscale and individual items from baseline (Visit 3, Day -1) to Day 42 (Visit 7) will also be analyzed in an exploratory manner, using the MMRM model without imputation similar to the one used in sensitivity analysis (2) for the primary efficacy endpoint described in Section 5.4.1.3. Anhedonia score is the sum of MADRS items 1 (reported sadness), 2 (apparent sadness), 6 (concentration difficulties), 7 (lassitude), and 8 (inability to feel).

5.6.4. Change in MADRS Total Score from Baseline to Day 42, in DGM4-Negative Patients

The change in MADRS total score from baseline to Day 42 (Visit 7) in DGM4-negative patients will be summarized using descriptive statistics.

5.6.5. Change in MADRS Total Score from Baseline to Day 42 in Liafensine 1 mg QD Group and 2 mg QD Group, in both DGM4-Positive and DGM4-Negative Patients

The change in MADRS total score from baseline to Day 42 (Visit 7) in liafensine 1 mg and 2 mg QD groups in both DGM4-positive and DGM4-negative patients will be analyzed using descriptive statistics. The treatment effects between the DGM4-positive and negative patients will be compared primarily in descriptive fashion to examine the trend and may be evaluated by including the interaction of DGM4 status and treatment group in the mixed model.

5.7. Pharmacokinetics

5.7.1. Plasma Concentrations

Plasma concentrations of liafensine and its major metabolite 821007 will be listed by subject and time of collection.

6. CHANGES FROM ANALYSES PLANNED IN THE PROTOCOL

Changes from the protocol-specified analyses are listed in Table 4.

Table 4. Changes from Protocol-Specified Analyses

Protocol	SAP	Justification
Section 8.3.3.1: The family-wise type I error rate will be controlled at a fixed 1-sided alpha level of 0.025 using a closed testing procedure for multiple dose comparisons and multiple endpoint comparisons in DGM4-positive patients.	Section 3.7: All statistical tests for the treatment comparison of efficacy endpoints will be based on a 1-sided alpha level of 0.05.	In this Phase 2b study, the sample size was not powered for testing superiority with multiplicity adjustment for each dose.
Section 8.3.3: The primary efficacy analysis will be performed in DGM4-positive patients at 2-sided significance level of 0.05 using a mixed model for repeated measures (MMRM) that includes the fixed effects of treatment, visit (categorical covariate), treatment-by-visit interaction, baseline MADRS total score (continuous covariate), and region.	Section 5.4.1.2: The primary method will be mixed model for repeated measures (MMRM) with imputation assuming missing at random (MAR), ie, a hypothetical strategy per ICH E9(R1). Hence, missing values will be imputed with non-missing values in the same treatment group. A fully conditional specification and predictive mean matching method will be used in the imputation. The following variables will be included in the imputation model: region, baseline MADRS score, and change from baseline at Weeks 1, 2, 4, and 6. One hundred fully imputed datasets will be created. The MMRM described in Section 5.4.1.2 will be used for treatment comparisons. Treatment effects (difference in LS means between treatment arms) from these 100 analyses will be combined to generate the final results using Rubin's method with SAS MIANALYZE procedure.	• With multiple imputation, all subjects in the full analysis set will have a value at the primary time point, ie, Day 42, for treatment comparisons. • Since the original method in the protocol assumes missing at random, the same assumption will be used in multiple imputation. • This method allows for performing a tipping point analysis to assess the robustness of the results under the MAR assumption.

7. REFERENCES

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8. APPENDIX: SAMPLE SAS CODES

The sample SAS codes provided in this section are for reference only. The actual SAS codes to generate the tables will be checked through QC process. For sensitivity analyses using RAS, use the dataset flag for RAS and exclude GPN*base, ie, treatment-by-baseline-score interaction, in the model statement in Proc Mixed.

8.1. SAS Code for Multiple Imputations Based on the Non-missing Values in the Same Arm with FCS and REGPMM Options

```
%let nimpute=100;
%let seed=10401;
proc sort data=adqs4 out=adqs5 ;
 where avisitn in (40 50 60 70) and dgmn=1 and gpn^=3;
 by trt01pn usubjid dgmn gpn region base avisitn;
run;
proc transpose data=adqs5 out=cfb;
  by GPN usubjid dgmn  region base;
  var chg;
  id avisitn;
run;
*** Imputation using fully conditional specification and predictive mean matching methods;
proc mi data=cfb(rename=(_40=cfb1 _50=cfb2 _60=cfb4 _70=cfb6))  nimpute=&nimpute
seed=&seed out=fcs;
   by GPN;
   class region;
   var region base cfb1 cfb2 cfb4 cfb6;
   FCS REGPMM;
run;
```

8.2. SAS Code for Treatment Comparisons in MMRM

Note: The SAS code below is for MMRM after multiple imputations. For MMRM without imputations, use the same code for data before imputation without "by _imputation_".

```
%let alpha=0.10;
data fcs2;
 set fcs;
 avisitn=40; CHG=cfb1; output;
 avisitn=50; CHG=cfb2; output;
 avisitn=60; CHG=cfb4; output;
 avisitn=70; CHG=cfb6; output;
proc sort data=fcs2;
 by _imputation_;
run;
proc mixed data=fcs2;
 by _imputation_;
 class GPN avisitn region usubjid;
```

```
        model CHG=GPN base AVISITN   GPN*AVISITN  GPN*base region/alpha=&alpha
DDFM = KR;
   repeated AVISITN/sub=usubjid type=UN;
*** contrasts for treatment comparisons;
        lsmestimate GPN*AVISITN 'LSMean Active Pooled Visit 40' 0.5 0 0 0  0.5 0 0 0  0 0 0
0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine 1 mg QD Visit 40' 1 0 0 0  0 0 0 0  0 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine 2 mg QD Visit 40' 0 0 0 0  1 0 0 0  0 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine Placebo Visit 40' 0 0 0 0  0 0 0 0  1 0 0
0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Liafensine 1 mg QD vs. placebo Visit 40' 1 0 0 0  0 0 0 0  -
1 0 0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Liafensine 2 mg QD vs. placebo Visit 40' 0 0 0 0  1 0 0 0  -
1 0 0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Active Pooled vs. placebo Visit 40' 0.5 0 0 0  0.5 0 0 0  -1 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Active Pooled Visit 50' 0 0.5 0 0  0 0.5 0 0  0 0 0
0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine 1 mg QD Visit 50' 0 1 0 0  0 0 0 0  0 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine 2 mg QD Visit 50' 0 0 0 0  0 1 0 0  0 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine Placebo Visit 50' 0 0 0 0  0 0 0 0  0 1 0
0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Liafensine 1 mg QD vs. placebo Visit 50' 0 1 0 0  0 0 0 0  0
-1 0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Liafensine 2 mg QD vs. placebo Visit 50' 0 0 0 0  0 1 0 0  0
-1 0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Active Pooled vs. placebo Visit 50' 0 0.5 0 0  0 0.5 0 0  0 -1
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Active Pooled Visit 60' 0 0 0.5 0  0 0 0.5 0  0 0 0
0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine 1 mg QD Visit 60' 0 0 1 0  0 0 0 0  0 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine 2 mg QD Visit 60' 0 0 0 0  0 0 1 0  0 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine Placebo Visit 60' 0 0 0 0  0 0 0 0  0 0 1
0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Liafensine 1 mg QD vs. placebo Visit 60' 0 0 1 0  0 0 0 0  0
0 -1 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Liafensine 2 mg QD vs. placebo Visit 60' 0 0 0 0  0 0 1 0  0
0 -1 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Active Pooled vs. placebo Visit 60' 0 0 0.5 0  0 0 0.5 0  0 0
-1 0/CL alpha=&alpha;
```

```
        lsmestimate GPN*AVISITN 'LSMean Active Pooled Visit 70' 0 0 0 0.5  0 0 0 0.5  0 0 0
0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine 1 mg QD Visit 70' 0 0 0 1  0 0 0 0  0 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine 2 mg QD Visit 70' 0 0 0 0  0 0 0 1  0 0
0 0/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'LSMean Liafensine Placebo Visit 70' 0 0 0 0  0 0 0 0  0 0 0
1/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Liafensine 1 mg QD vs. placebo Visit 70' 0 0 0 1  0 0 0 0  0
0 0 -1/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Liafensine 2 mg QD vs. placebo Visit 70' 0 0 0 0  0 0 0 1  0
0 0 -1/CL alpha=&alpha;
        lsmestimate GPN*AVISITN 'Active Pooled vs. placebo Visit 70' 0 0 0 0.5  0 0 0 0.5  0 0
0 -1/CL alpha=&alpha;
  lsmeans GPN*avisitn/CL alpha=&alpha pdiff;
  ods output diffs=diffs1 lsmeans=lsmean1 tests3=tests3 convergenceStatus=convg
LSMEstimates=LSM;
run;
```

8.3. SAS Code for Summarizing Treatment Comparison Results from Multiple Imputations Using Proc MIANALYZE

```
*** Analysis result from imputation and MIANALYZE - for CSR table;
%let alpha=0.10;
proc sort data=lsm;
 by label _imputation_;
run;
proc mianalyze data=lsm alpha=&alpha;
  by label ;
   modeleffects ESTIMATE;
   stderr stderr;
    ods output ParameterEstimates=PARA;
run;
```

8.4. SAS Code for Imputation Using Non-missing Values in the Control Arm

```
proc sort data=adqs4 out=adqs5 ;
 where avisitn in (40 50 60 70) and dgmn=1 and gpn^=3;
 by trt01pn usubjid dgmn gpn region base avisitn;
run;
proc transpose data=adqs5 out=cfb;
  by GPN usubjid dgmn  region base;
  var chg;
  id avisitn;
run;
```

```
*** Pattern-Mixture imputation using fully conditional specification and predictive mean
matching methods;
proc mi data=cfb(rename=(_40=cfb1 _50=cfb2 _60=cfb4 _70=cfb6))  nimpute=&nimpute
seed=&seed out=fcs;
  class gpn region;
  FCS REGPMM;
  mnar model(cfb1 cfb2 cfb4 cfb6/modelobs=(gpn='4'));
*** gpn='4': control arm;
  var region base cfb1 cfb2 cfb4 cfb6;
run;
data fcs2;
 set fcs;
 avisitn=40; CHG=cfb1; output;
 avisitn=50; CHG=cfb2; output;
 avisitn=60; CHG=cfb4; output;
 avisitn=70; CHG=cfb6; output;
proc sort data=fcs2;
 by _imputation_;
run;
```

8.5. SAS Code for Imputation Using Non-missing Values in the Control Arm or the Same Arm per Intercurrent Events

The SAS code will follow the algorithm below.

1) Pool subjects who terminated early due to AE in all 3 arms and subjects in the placebo arm. This dataset will also include placebo subjects with missing values due to withdrawal of consent to treatment, other/lost to follow-up, or pregnancy, but will exclude early terminators due to death.

2) For the pooled datasets in 1), use sample SAS code below to impute missing values based on non-missing values in the place arm to create 100 datasets.

```
proc mi data=cfb0(rename=(_40=cfb1 _50=cfb2 _60=cfb4 _70=cfb6))
nimpute=&nimpute seed=&seed out=ras0;
  class gpn region;
  FCS REGPMM;
  mnar model(cfb1 cfb2 cfb4 cfb6/modelobs=(gpn='4'));
*** gpn='4': control arm;
```

3) Select subjects in the 1 mg group by excluding early terminators due to AE or death. This dataset will include subjects without missing values and subjects with missing values due to withdrawal of consent to treatment, other/lost to follow-up, or pregnancy.

4) For the datasets in 3), use sample SAS code below to impute missing values based on non-missing values in the same arm to create 100 datasets.

```
proc mi data=cfb1(rename=(_40=cfb1 _50=cfb2 _60=cfb4 _70=cfb6))
nimpute=&nimpute seed=&seed out=ras1;
  class nonm region;
```

```
  FCS REGPMM;
  mnar model(cfb1 cfb2 cfb4 cfb6/modelobs=(nonm='1'));
***Variable nonm=1: completers;
  var region base cfb1 cfb2 cfb4 cfb6;
run;
```

5) Repeat steps 3) and 4) for the 2 mg group and name the imputed datasets as ras2.

6) One death with unknown reason and un-determined relationship to study drug occurred in this study. Missing data prior to death will be imputed based on the worst score from this subject, and data after death will not be imputed. Multiple imputations will be carried out using a normal random variable with mean equal to the worst score in the schedule visits of this subject, and variance equal to the observed variance from the same treatment arm at the same visit.

   SAS function RAND('NORMAL', W, SD) will be used to generate 100 values for each missing data, where W is the worst change from baseline value of this subject and SD is the standard deviation for the visit from the same arm.

```
call streaminit(10401);
  do i=1 to 100;
    cfb= RAND('NORMAL', W, SD)
    output;
  end;
```

   Name the imputed dataset for this subject as ras3.

7) Pool datasets ras0, ras1, ras2, and ras3 together, sort by imputation number, and perform treatment comparisons using sample SAS code in Section 8.2.

8) Use sample SAS code in Section 8.3 to summarize and finalize the treatment comparison results.

8.6. SAS Code for Imputation Pertaining to Use of Prohibited Medications

In Sensitivity analysis 3 in Section 5.4.1.3, data collected after initiation of prohibited medications will not be used. They will be imputed using non-missing values in the placebo arm. SAS code in Section 8.4 will be used.

In Sensitivity analysis 4 in Section 5.4.1.3, data after initiation of prohibited medication will be imputed with non-missing data in the same arm while the subject is on study medication. If the subject terminates study medication early after initiation of prohibited medication, missing data after treatment termination will be imputed according to the cause of termination. Two scenarios may occur as follows:

1) The subject initiated prohibited medication and completed the treatment period. Imputation of data after initiation of prohibited medication will be the same as imputing missing data in Group 2 in Sensitivity analysis 4, and the SAS code in Section 8.5 will be applied.

2) The subject initiated prohibited medication and terminated the treatment early. If the cause of termination is in Group 2 in Sensitivity analysis 4, the imputation will be same as in 1). If the reason for termination is in Groups 1 or 3, the following steps will be followed.

    a. Impute data after initiation of prohibited medication as in 1).
    b. Set imputed data after termination as missing.
    c. If the cause of termination is death, impute data using the method stated in 6) in Section 8.5.
    d. If early termination is due to AE, perform a second set of imputation for data after early termination based on non-missing data in the placebo arm.

8.7. SAS Code for Tipping Point Analysis

The SAS code will follow the algorithm below.

1) Impute missing values per SAP to create 100 datasets.
2) In each dataset, create a variable MIFL (imputation flag) to indicate whether a data point was imputed or not.
3) Increase or decrease each imputed value per macro parameter for each arm.
4) For each dataset, perform treatment comparisons using LSMESTIMATE statements in Proc Mixed.
5) Use Proc MIANALYZE to summarize the final result from the analysis of the 100 datasets.

```
%macro Tipping(indata=, cfb=, gp1=, gp2, gp4=, outdata=);
*** Indata=input dataset from steps 1) and 2) above. For each imputed dataset, the data structure should be one observation per subject per visit.
        Cfb=variable name for change from baseline value
        gp1=imputed data to be shifted in the 2 mg arm
        gp2=imputed data to be shifted in the 1 mg arm
        gp4=imputed data to be shifted in the placebo arm
        outdata=output dataset for the final result from Proc MIANALYZE;
data a;
 set &indata;
if MIFL='Y' then
do;
        if GPN=1 then &cfb=&cfb + (&gp1);
        else if GPN=2 then &cfb=&cfb + (&gp2);
        else if GPN=4 then &cfb=&cfb + (&gp4);
end;
*** Include SAS code in Section 8.2 to perform treatment comparisons.
*** Include SAS code in Section 8.3 to use Proc MIANALYZE to summarize the final result from the analysis of the 100 datasets and output the final result to dataset &outdata.
%mend;
```

8.8. SAS Code for Stratified CMH Test

```
*** CMH test for pooled analysis stratified by region;
*** gpn=3: both active arms pooled, gpn=4: placebo arm;
*** For 1 mg vs. placebo and 2 mg vs. placebo, replace 3 with 1 and 2, respectively.;
proc freq data=adqs4(where=(gpn in (3 4) and dgmn=3 and avisitn=70));
  table region*GPN*aval / CMH ALPHA=0.10;
run;
```