Janssen Research & Development

Statistical Analysis Plan

A Randomized, Open-Label, Rater-Blinded, Active-Controlled, International, Multicenter Study to Evaluate the Efficacy, Safety and Tolerability of Flexibly Dosed Esketamine Nasal Spray Compared with Quetiapine Extended-Release in Adult and Elderly Participants with Treatment-Resistant Major Depressive Disorder who are Continuing a Selective Serotonin Reuptake Inhibitor/Serotonin-Norepinephrine Reuptake Inhibitor

ESCAPE-TRD

Protocol 54135419TRD3013; Phase 3b

JNJ-54135419 (esketamine)

Status: Approved
Date: 12 September 2022
Prepared by: PPD / Janssen Research & Development, LLC), PPD (CRO Valos J&J partner)
Document No.:

TABLE OF CONTENTS

VERSION HISTORY

Table: SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	17 December 2021	Not Applicable	Initial release
2	12 September 2022	Update use of Visit Windows	Small changes
		Add handling of missing data for primary endpoint and key secondary endpoint	Clarification
		Time to relapse: calculation	Clarification
		Time to relapse: add Kaplan-Meier analysis	Additional analysis
		CMH test: in main analysis CRF data will be used for stratification factors, in sensitivity analysis IXRS data will be used	Clarification
		MMRM analysis: add overall analysis	Additional analysis
		Sensitivity analysis for remission/relapse over time	Added sensitivity analysis

1. INTRODUCTION

This statistical analysis plan describes the definitions of analysis sets, derived variables, and statistical methods for all planned statistical analyses to be documented in the CSR for protocol 54135419TRD3013. Additional (abbreviated) SAPs will be developed for various supplementary and post-hoc analyses.

1.1. Objectives and Endpoints

Primary objective

The primary objective of this study is to evaluate the efficacy of flexibly dosed esketamine nasal spray compared with quetiapine extended-release (XR), both in combination with a continuing selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI), in achieving remission in participants who have treatment-resistant MDD with a current moderate to severe depressive episode. Remission at the Week 8 visit is defined as a Montgomery-Asberg Depression Rating Scale (MADRS) total score of ≤10.

Key secondary objective

The key secondary endpoint is to assess the efficacy of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in the proportion of participants being relapse-free at Week 32 after remission at Week 8. The key secondary parameter is defined as remission at Week 8 visit (ie, MADRS total score of ≤10 at the end of Week 8) and no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit.

Note: A relapse is defined by any of the following:

a) Worsening of depressive symptoms as indicated by MADRS total score ≥22 confirmed by 1 additional assessment of MADRS total score ≥22 within the next 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse.

b) Any psychiatric hospitalization for:

   - worsening of depression;
   - suicide prevention or due to a suicide attempt.

   For any of these events, the start date of hospitalization will be used for the date of relapse.

c) Suicide attempt, completed suicide, or any other clinically relevant event determined per the investigator's clinical judgment to be indicative of a relapse of depressive illness, but for which the participant was not hospitalized. The onset of the event will be used for the date of relapse.

In case more than 1 of the relapse criteria are met, the earliest date will be defined as the date of relapse for that participant.

Other secondary objectives

To assess the effect of esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in:

- Clinician-rated overall severity of depressive illness;

- Early onset of action;
- Clinician-rated depressive symptoms;
- Participant-reported depressive symptoms;
- Participant-reported functional impairment and associated disability;
- Participant-reported health-related quality of life and health status;
- Participant-reported work productivity;
- Safety and tolerability.

Exploratory objective

To assess the potential relationship of biomarkers with response/non-response to study intervention in participants with treatment resistant MDD.

1.2. Study Design

Study design and patient selection

This is a randomized, open-label, rater-blinded, active-controlled, international, multicenter study in participants 18 to 74 years of age, inclusive, with treatment-resistant MDD.

To be eligible for enrollment in the study:

- Participant must be on a *current* antidepressive treatment that includes an SSRI/SNRI at screening that resulted in nonresponse (less than 25% improvement of symptoms) after having been given at an adequate dosage (been uptitrated to maximum tolerated dose; based on antidepressive dosages from Summary of Product Characteristics [SmPC; or local equivalent, if applicable]) for an adequate duration of at least 6 weeks; however, at screening the participant must show signs of minimal clinical improvement to be eligible for the study.
- In addition to the current antidepressive treatment, participant must have documented nonresponse within the current moderate to severe depressive episode to at least 1 but not more than 5 different, previous consecutive treatments with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks and that each prior AD treatment did not produce any significant improvement (less than 25% improvement of symptoms).
- Participant must have been treated with at least 2 different antidepressive substance classes among the failed treatments in the current moderate to severe depressive episode (including the current treatment with an SSRI/SNRI).
- Participant must be on a single oral SSRI/SNRI on Day 1 prior to randomization.

Study phases

The study has 4 phases: an up-to-14-day screening phase, an 8-week acute phase, a 24-week maintenance phase, and a 2-week safety follow-up phase. During the acute phase, participants in the esketamine arm will have twice-weekly visits from Week 1 to Week 4 and once-weekly visits from Week 5 to Week 8; during the maintenance phase from Week 9 to Week 32, visits will be once weekly or every 2 weeks (even weeks) based on dosing. Participants in the comparator arm will have weekly visits from Week 1 to Week 4, and then every 2 weeks for the remainder of the acute phase (Week 6 and Week 8) and the maintenance phase (Week 10, Week 12, etc) through Week 32. All participants have a safety follow-up visit 2 weeks following the last dose of study

intervention. Participants who discontinue the study intervention early (ie, discontinue either component of the randomized combination therapy) will remain in the study and continue to return for all follow-up visits through Week 32, according to the Schedule of Activities.

For participants in the esketamine arm:

At the Week 4 visit, evidence of therapeutic benefit of the study intervention (ie, esketamine nasal spray in combination with a continuing SSRI/SNRI) will be evaluated clinically by the investigator. In the evaluation of therapeutic benefit, the full scope of clinical improvement should be evaluated including any improvement in depressive symptoms, general functioning, social functioning, and self-care. If there is no evidence of therapeutic benefit, the investigator and the participant should discuss the treatment strategy and mutually agree on whether to continue or discontinue esketamine nasal spray.

Beginning at the Week 8 visit, all participants in both study intervention arms will undergo regular assessments of symptom changes from baseline (ie, treatment continuation assessment) to ensure that study intervention continuation is appropriate. This will be operationalized using the CGI-C clinician-rated scale (referring to study baseline [Day 1]) every 4 weeks, and treatment decisions will be made using cut-off values below.

Treatment Continuation Assessment of Study Intervention	
CGI-C ≥4 ("no change" or worse) at 2 consecutive visits	Recommendation to reconsider appropriateness of study intervention and to switch to an alternative standard-of-care treatment.
CGI-C <4 ("Minimally improved" or better) at any visit	Study intervention may be continued at the discretion of the investigator.
CGI-C= Clinical Global Impression – Change Note: After early discontinuation of study intervention, the CGI-C will still be performed at follow-up visits according to the Schedule of Activities; however, treatment decisions will be at the discretion of the investigator and not based on the criteria for the treatment continuation assessment.	

Randomization

A total of 622 participants will be randomly assigned on Day 1 (baseline) in a 1:1 ratio to 1 of 2 open-label study intervention arms (311 participants per arm). The randomization will be balanced by using randomly permuted blocks and will be stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more [inclusive of current antidepressive treatment at screening used to determine eligibility]).

Esketamine arm

Participants will continue to take their current SSRI/SNRI in combination with esketamine nasal spray.

On Day 1, participants will have their first nasal treatment session. Adult participants aged 18 to 64 years will start with a dose of 56 mg. Elderly participants aged 65 to 74 years and adults of Japanese ancestry will start with a dose of 28 mg. As of Day 4, the dose may be increased from 56 mg to 84 mg in adult participants, from 28 mg to 56 mg in elderly participants and adults of

Japanese ancestry, or participants may remain at the starting dose, as determined by the investigator based on efficacy and tolerability. Elderly participants and adults of Japanese ancestry may be uptitrated in 28 mg increments at subsequent visits. The highest dose that may be used in all participants is 84 mg. Nasal treatment sessions will occur twice weekly during Week 1 to Week 4, once weekly during Week 5 to Week 8, and once weekly or every 2 weeks, as determined by the investigator based on efficacy and tolerability, during the maintenance phase (Week 9 to Week 32). Dosing may be increased at any visit, may remain the same, or may be reduced as determined by the investigator based on efficacy and tolerability. Nasal treatment sessions should not take place on 2 consecutive days. Esketamine nasal spray dosing and related safety-monitoring procedures MUST be performed LAST at all visits. Esketamine nasal spray must NOT be administered before all other visit assessments are completed. Food will be restricted for at least 2 hours before each administration of esketamine nasal spray. Drinking of any fluids will be restricted for at least 30 minutes before the first nasal spray at each session.

Comparator Arm

Participants will continue to take their current SSRI/SNRI which will be augmented with quetiapine XR as per the SmPC (or local equivalent, if applicable) starting on Day 1 and will continue through Week 32. In adult participants aged 18 to 64 years, the initial dose of quetiapine XR is 50 mg/day on Days 1-2, 150 mg/day on Days 3-4 [lowest effective dose]; a further dose increase to 300 mg/day as of Day 5 will be based on individual participant evaluation. In elderly participants aged 65 to 74 years, the initial dose is 50 mg/day on Days 1-3, 100 mg/day on Days 4-7, and 150 mg/day on Day 8; a further dose increase to 300 mg/day will be based on individual participant evaluation no earlier than Day 22. If participants cannot tolerate at least 150 mg/day of quetiapine XR by the end of Week 2 (or at any subsequent time during the study), they must have quetiapine XR discontinued.

Continuing SSRI/SNRI

The continuing SSRI/SNRI being taken by a participant must be labeled for treatment of depression/MDD in their country of participation and the dosage being taken should be according to the respective SmPC (or local equivalent, if applicable). Off-label use of an SSRI/SNRI is not permitted. The investigator may optimize the dose of the continuing SSRI/SNRI, up to the maximum tolerated dose as per the respective SmPC (or local equivalent, if applicable). Once optimized, a stable dose should be maintained; however, dose modifications may be made, if necessary, at the investigator's discretion.

Treatment discontinuation

The study intervention will be considered discontinued if either component of the randomized combination therapy (ie, esketamine nasal spray, quetiapine XR, or continuing SSRI/SNRI) is stopped. If esketamine nasal spray or quetiapine XR is discontinued at any time during the acute or maintenance phase, the participant will be switched to an alternative standard of care treatment, which may or may not include the continuing SSRI/SNRI, at the discretion of the investigator and continue follow-up visits through Week 32. If determined by the investigator that the alternative standard of care will include esketamine nasal spray (when commercially available in country of participation) or quetiapine XR for a participant, it will not be provided to the participant, rather,

the investigator must prescribe the medication to the participant. If the SSRI/SNRI is discontinued at any time during the acute or maintenance phase, the esketamine nasal spray or quetiapine XR must also be discontinued. The participant will be switched to an alternative standard of care treatment at the discretion of the investigator and continue follow-up visits through Week 32.

2. STATISTICAL HYPOTHESES

The primary hypothesis of this study is that among participants who have treatment-resistant MDD with a current moderate to severe depressive episode, the proportion of participants achieving remission at the Week 8 visit is greater in participants treated with flexibly dosed esketamine nasal spray than in participants treated with quetiapine XR, both administered in combination with a continuing SSRI/SNRI.

The key secondary hypothesis of this study is that among participants who have treatment-resistant MDD with a current moderate to severe depressive episode, the proportion of participants who achieved remission at the Week 8 visit and remain relapse-free through the Week 32 visit is greater in participants treated with esketamine nasal spray than in participants treated with quetiapine XR, both administered in combination with a continuing SSRI/SNRI.

3. SAMPLE SIZE DETERMINATION

For the primary endpoint, the assumptions are that the rate of remission for completers at the Week 8 visit is 50% in the esketamine arm and 35% in the comparator arm, and that the rate for participants who discontinue study intervention between baseline and the Week 8 visit is 17.5% in both treatment arms (to be imputed as non-remitters). Combining these assumptions leads to an estimated remission rate at the Week 8 visit in non-responder imputation (NRI) analysis of 41.25% in the esketamine arm and 28.88% in the comparator arm. With a power of 90%, a 2-sided significance level of 0.05 and using chi-square test, a sample size of 311 participants per arm (622 participants in total) is needed to detect the difference between the study intervention arms.

For the key secondary endpoint, among participants who achieve remission at the Week 8 visit, a relapse rate of 30% is assumed for both study intervention arms and rates for participants who discontinue study intervention between the Week 8 and Week 32 visits (to be imputed as non-relapse-free after remission) is assumed to be 10% for the esketamine arm and 20% for the comparator arm. Combining these assumptions leads to an estimated rate of relapse-free after remission at the Week 32 visit in NRI analysis of 25.99% in the esketamine arm and 16.17% in the comparator arm. With a power of 80%, a 2-sided significance level of 0.05 and using a chi-square test, a sample size of 270 randomized participants per arm (540 participants in total) is needed to detect a difference between the study intervention arms.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The following analysis sets will be used in this SAP:

Analysis Sets	**Description**
Enrolled Analysis Set	All participants who sign the ICF
Full Analysis Set (FAS)	The full analysis set includes all randomized participants.

Analysis Sets	Description
Safety Analysis Set	The safety analysis set includes all randomized participants who received at least 1 dose of any study intervention.
Follow-up Analysis Set	The follow-up analysis set includes all randomized participants who received at least 1 dose of any study intervention, and who discontinue study intervention.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits (or data collection dates) to analysis visits. The reference day is Study Day 1 (Baseline). If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the analysis visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. In Excel sheet "*Visit_windows_v3.xlsx*" are the analysis visit windows and the target days for each visit associated to the different parameters defined in the protocol.

The above procedure will be used for all visits except for the Week 8 visit and the Week 32 visit. For both Week 8 and Week 32 visit, the actual visit with the nominal visit label will be assigned to the corresponding analysis visit.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention
- Participants who completed the study

The number of participants in the following disposition categories will be summarized for the first 8 weeks of the study, for the second part (week 9-32) and overall, by intervention group:

- Participants who discontinued study intervention
- Reasons for discontinuation of study intervention
- Participants who terminated study prematurely
- Reasons for termination of study

A listing of participants will be provided for the following category:

- Participants who were randomized yet did not receive study intervention.

5.3. Primary Endpoint Analysis

5.3.1. Definition of Endpoint

The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The MADRS consists of 10 items that cover all of the core depressive symptoms (apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts). Each item is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptom). A total score (0 to 60) is calculated by adding the scores of all 10 items. For each item as well as the total score, a higher score represents a more severe condition. If 2 or more items are missing, no imputation will be performed, and the total score will be left missing. Otherwise, the total score will be calculated as the sum of the items present multiplied by the ratio of the maximum possible number of items (i.e., 10) to the number of items present.

The primary endpoint is remission at the Week 8 visit, defined as a MADRS total score of ≤10.

5.3.2. Estimand

Primary Trial Objective: to evaluate the efficacy of flexibly dosed esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in achieving remission at the Week 8 visit in participants who have treatment resistant MDD with a current moderate to severe depressive episode.

Estimand Scientific Question of Interest: What is the proportion of participants considered to have benefited from esketamine versus quetiapine XR for the pre-specified duration (8 weeks), administered in combination with a continuing SSRI/SNRI?

Study intervention:

- Flexibly dosed esketamine nasal spray in combination with a continuing SSRI/SNRI
- Quetiapine XR in combination with a continuing SSRI/SNRI**.**

Population: Participants

- 18 to 74 years of age (inclusive) with treatment resistant MDD
- on a current antidepressive treatment that includes an SSRI/SNRI that resulted in nonresponse, but the participant shows signs of minimal clinical improvement
- must have documented nonresponse within the current moderate to severe depressive episode to at least 1 but not more than 5 different, previous consecutive treatments with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks, and that each prior AD treatment did not produce any significant improvement
- must have been treated with at least 2 different antidepressive substance classes among the failed treatments in the current depressive episode.

Variable: Remission (binary variable), where remission is defined as a participant achieving a MADRS total score of ≤10 at the Week 8 visit, who does not before week 8 visit:

- discontinues (any component of) study intervention, or
- withdraws from the study.

Summary measure (population-level summary): Difference in proportions.

Intercurrent events and their corresponding strategies:

Intercurrent Events	*Strategy for Addressing Intercurrent Events and its Description*
Discontinuation of (any component of) study intervention for any reason	*Composite Strategy*: A participant with this intercurrent event is considered as a non-responder after this event, the occurrence of this intercurrent event being captured in the variable definition
Withdrawal from the study	*Composite Strategy*: Same as above

In the main analysis, for subjects who do not have an available MADRS result at the Week 8 visit but did not discontinue study intervention or withdraw from study before Week 8, LOCF of MADRS will be applied. In a sensitivity analysis, these subjects will be considered a non-responder.

5.3.3. Analysis Methods

The efficacy analysis of data will be based on the full analysis set. Statistical analysis test will be conducted at a two-sided 0.050 level of significance.

The rate of remission at the Week 8 visit will be tested between study intervention arms using a Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more). The estimate of the treatment difference in proportions, the odds ratio and their 95% CI will be reported. In the main analysis, the variables age and number of treatment failures will be based on CRF data. A sensitivity analysis will be performed using IXRS data.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Key Secondary Endpoint

5.4.1.1. Definition of Endpoint

A relapse is defined by any of the following:

a) Worsening of depressive symptoms as indicated by MADRS total score ≥22 confirmed by 1 additional assessment of MADRS total score ≥22 within the next 5 to 15 days. The date of the second MADRS assessment will be used for the date of relapse.

b) Any psychiatric hospitalization for

   a. worsening of depression
   b. suicide prevention or due to a suicide attempt

For any of these events, the start date of hospitalization will be used for the date of relapse.

c) Suicide attempt, completed suicide, or any other clinically relevant event determined per the investigator's clinical judgment to be indicative of a relapse of depressive illness, but for which the participant was not hospitalized. The onset of the event will be used for the date of relapse.

In case more than 1 of the relapse criteria are met, the earliest date will be defined as the date of relapse for that participant.

The key secondary endpoint is remission at Week 8 visit (ie, MADRS total score of ≤10 at the end of Week 8) *and* no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit.

5.4.1.2. Estimand(s)

Key Secondary Trial Objective: to evaluate the efficacy of flexibly dosed esketamine nasal spray compared with quetiapine XR, both in combination with a continuing SSRI/SNRI, in achieving remission at the Week 8 visit *and* having no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit in participants who have treatment resistant MDD with a current moderate to severe depressive episode.

Estimand Scientific Question of Interest: What is the proportion of participants considered to have benefited from esketamine versus quetiapine XR for the pre-specified duration (32 weeks), administered in combination with a continuing SSRI/SNRI?

Study intervention:

- Flexibly dosed esketamine nasal spray in combination with a continuing SSRI/SNRI
- Quetiapine XR in combination with a continuing SSRI/SNRI**.**

Population: Participants

- 18 to 74 years of age (inclusive) with treatment resistant MDD
- on a current antidepressive treatment that includes an SSRI/SNRI that resulted in nonresponse, but the participant shows signs of minimal clinical improvement
- must have documented nonresponse within the current moderate to severe depressive episode to at least 1 but not more than 5 different, previous consecutive treatments with ADs taken at an adequate dosage for an adequate duration of at least 6 weeks, and that each prior AD treatment did not produce any significant improvement
- must have been treated with at least 2 different antidepressive substance classes among the failed treatments in the current depressive episode.

Variable: Week-32-response (binary variable), where week-32-response is defined as a participant achieving remission at the Week 8 visit (defined as a MADRS total score of ≤10) *and* having no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit, who does not:

- discontinues (any component of) study intervention, or
- withdraws from the study.

Summary measure (population-level summary): Difference in proportions.

Intercurrent events and their corresponding strategies:

Intercurrent Events	*Strategy for Addressing Intercurrent Events and Its Description*
Discontinuation of (any component of) study intervention for any reason	*Composite Strategy*: A participant with this intercurrent event is considered as a non-responder after this event, the occurrence of this intercurrent event being captured in the variable definition
Withdrawal from the study	*Composite Strategy*: Same as above

In the main analysis, for subjects who do not have an available MADRS result at the Week 8 visit but did not discontinue study intervention or withdraw from study before Week 8, LOCF of MADRS will be applied at Week 8. In a sensitivity analysis, these subjects will be considered to not be in remission at Week 8.

5.4.1.3. Analysis Methods

The efficacy analysis of data will be based on the full analysis set. Statistical analysis test will be conducted at a two-sided 0.050 level of significance.

The rate of remission at the Week 8 visit *and* having no relapse within the consecutive 24 weeks until the end of the prospective observation period at Week 32 visit will be tested between study intervention arms using a Cochran-Mantel-Haenszel (CMH) chi-square test adjusting for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more). The estimate of the treatment difference in proportions, the odds ratio and their 95% CI will be reported. In the main analysis, the variables age and number of treatment failures will be based on CRF data. A sensitivity analysis will be performed using IXRS data.

5.5. Supportive Secondary Endpoint(s)

5.5.1. General Analysis Methods

For continuous/ordinal parameters (eg, MADRS, CGI-S, PHQ-9, EQ-5D-5L, SF-36, SDS, WPAI:D) descriptive statistics of the score or values and change from baseline will be provided for each study visit during the study for the full analysis set. For CGI-C descriptive statistics of the score will be provided for each study visit during the study by study intervention for the full analysis set. Summaries of both observed and last observation carried forward (LOCF) data will be presented. The change from baseline at each visit will be analyzed using a mixed model for repeated measurements based on observed cases. The model will include baseline score as a covariate, and study intervention, stratification factors (age [18 to 64 years (inclusive); 65 to 74 years (inclusive)] and total number of treatment failures [2; 3 or more]), visit, and visit-by-study intervention interaction as fixed effects applying an unstructured covariance matrix. In case of issue with convergence of the model, alternative structures of variance-covariance matrix will be tested. The change from baseline at each visit will also be analyzed using an analysis of covariance model including LOCF data with factors for treatment, stratifications factors (age [18 to 64 years

(inclusive); 65 to 74 years (inclusive)] and total number of treatment failures [2; 3 or more]) and baseline score as a covariate. For all model approaches, LS estimates of the treatment differences at each visit and 95% confidence intervals will be presented. Additionally, for the MMRM model, the LS mean change from baseline averaged over all visits will be presented with 95% confidence interval per treatment group. The corresponding treatment difference will be presented with 95% confidence interval and two-sided p-value.

Additionally, for scales that have a minimum clinically important difference (MCID), the proportion of participants having improved by at least the MCID will be described at each visit and compared between study interventions using CMH chi-square test adjusting for age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and total number of treatment failures (2; 3 or more). The same analysis will be conducted for the proportion of participants who deteriorate by at least the MCID.

Time to event parameters (eg, time to improvement by at least MCID) will be analyzed by the Kaplan-Meier method and study interventions will be compared using a 2-sided log-rank test for the full analysis set. Time to event will be summarized with median, 25th and 75th percentile (if estimable). Confidence intervals of 25th, 50th, and 75th percentile of time to event will also be provided. Hazard ratios and their confidence intervals will be estimated using Cox proportional hazard models stratified by age (18 to 64 years [inclusive]; 65 to 74 years [inclusive]) and number of previous treatment failures (2; 3 or more).

5.5.2. Montgomery-Asberg Depression Rating Scale (MADRS)

Definitions

The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items, each of which is scored from 0 (item is not present or is normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, interest level, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

If 2 or more items are missing, no imputation will be performed, and the total score will be left missing. Otherwise, the total score will be calculated as sum of the non-missing items multiplied by the ratio of the maximum number of items (i.e., 10) to the number of non-missing items.

A subject is defined as a responder at a given time point if the percent improvement in MADRS total score from baseline is ≥ 50% or if the MADRS total score is ≤10.

A subject is defined as being in remission at a given time point if the MADRS total score is ≤10.

Rating of the MADRS will be conducted face-to-face with the participants by an independent rater. However, there may be situations where the rating is done remotely. The proportion of ratings by type of contact (site visit, home visit, remote video call) will be summarized by visit and study intervention.

Analysis Methods

See section 5.5.1 for the analysis of the MADRS total score.

The proportion of subjects who responded and who are in remission will be summarized for each scheduled visit with N and % in each category by study intervention. Summaries of both observed and LOCF data will be presented. Stacked bar graphs will be made to show the proportion of subjects who are in remission and who responded but not in remission over time. In a sensitivity analysis, the proportions will be calculated with observed data in the numerator and the full analysis set in the denominator.

5.5.3. Relapse

Definitions

The definition of relapse is described in section 5.4.1.1.

The remission time point is the first time point at which the participant is in remission. The time to first relapse will be calculated from the remission time point until the date of first relapse.

Analysis Methods

This analysis will only include participants for whom the remission time point is before or at Week 8. The number of patients with a relapse and the reason(s) for relapse, being 'MADRS total score >=22 for 2 assessments separated by 5 to 15 days'; 'subject been hospitalized for worsening of depression, or for suicide prevention or due to a suicide attempt'; 'Has there been a suicide attempt, completed suicide or any other clinically relevant event determined per the investigator's clinical judgement to be indicative of a relapse of depressive illness, but for which the participant was not hospitalized', will be summarized with N and % in each category by study intervention.

The time to first relapse will be summarized with descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]). Time to first relapse (from remission time point) will be analyzed by the Kaplan-Meier method. Time to relapse will be summarized with median, 25th and 75th percentile (if estimable). Confidence intervals of 25th, 50th, and 75th percentile of time to relapse will also be provided.

The relapse narratives will be listed.

5.5.4. Clinical Global Impression – Severity (CGI-S)

Definitions

The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience, a subject is assessed on severity of mental illness at the time of rating according to: 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.

Analysis Methods

See section 5.5.1 for the analysis of the CGI-S score.

In addition, a frequency distribution will be provided for each scheduled visit. Summaries of both observed and LOCF data will be presented.

5.5.5. Clinical Global Impression – Change (CGI-C)

Definitions

The CGI-C evaluates the total improvement whether or not due entirely to drug treatment on a scale of 1 to 7. Compared to the condition at baseline, a subject is assessed on how much he/she has changed, according to: 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse.

Analysis Methods

A frequency distribution will be provided for each scheduled visit. Summaries of both observed and LOCF data will be presented.

5.5.6. Therapeutic benefit assessment (esketamine arm)

Definitions

The therapeutic benefit assessment at visit week 4 for the esketamine receiving subjects consists of 3 Yes/No questions: "Did the evaluation of therapeutic benefit take place?", "Was there evidence of therapeutic benefit?" and "Was the treatment with esketamine continued?". If there was no evidence of therapeutic benefit *and* the treatment with esketamine continued, the reason is reported as: "Longer time to response / remission expected", "Negative life event / unstable life circumstances", "Other".

Analysis Methods

A frequency distribution will be provided for each question. The specifications of reason "Other" will be listed.

5.5.7. Treatment Continuation Assessment

Definitions

The treatment continuation assessment is scheduled for every 4 weeks starting as of visit week 8. The treatment decision is based on the CGI-C value of the visit, and is recorded as "Study intervention continued", "Study intervention not continued and switch to alternative SoC". The reason for continuation of study intervention in case of CGI-C >4 at 2 consecutive visits is recorded as: "Patient's preference", "Longer time to response/remission is expected", "Negative life event/unstable life circumstances", "Lack of alternative treatment option", "Other".

Analysis Methods

A frequency distribution will be provided for each question for each scheduled visit. The specifications of reason "Other" will be listed.

5.5.8. Patient Health Questionnaire – 9 item (PHQ-9)

Definitions

The PHQ-9 is a validated 9-item, PRO measure to assess depressive symptoms. Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The participant's item responses are summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. In addition, the question "If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?" is scored as "Not difficult at all", "Somewhat difficult", "Very difficult", "Extremely difficult".

A subject is defined as a responder at a given time point if the percent improvement from baseline in PHQ-9 total score is ≥ 50%.

A subject is defined as a remitter at a given time point if the PHQ-9 total score is ≤9 at that time point.

Analysis Methods

See section 5.5.1 for the analysis of the PHQ-9 total score.

Frequency distributions will be provided for the addition question on the PHQ-9, PHQ-9 response and PHQ-9 remission for each scheduled visit. Summaries of both observed and LOCF data will be presented.

5.5.9. Quality of Life in Depression Scale (QLDS)

Definitions

The QLDS is a disease-specific validated PRO measure which assesses the impact that depression has on a participant's quality of life. It is a 34-item self-rated questionnaire which consists of dichotomous response questions, with the response being either True/Not True. Each statement on the QLDS is given a score of "1" or "0". A score of "1" is indicative of adverse quality of life. All item scores are summed to give a total score that ranges from 0 (good quality of life) to 34 (very poor quality of life). As the measure contains positive as well as negative items, item scores are not always in the same order - that is, not all 'true' responses are allocated a score of "1". Listed below are the statements with the alternative responses and their associated scores:

I just want time to pass	True	1
	Not true	0
I feel hopeful about the future	True	0
	Not true	1
I find it hard to hold a conversation	True	1
	Not true	0
I like to know what is going on in the world	True	0
	Not true	1
I feel as if my life is wasting away	True	1
	Not true	0
I feel as if I am not in control of my life	True	1
	Not true	0
I am reluctant to leave the house	True	1
	Not true	0
On the whole, I enjoy the things I do	True	0
	Not true	1
I have lost all pleasure in life	True	1
	Not true	0
I feel as if I have nothing to offer anyone	True	1
	Not true	0
I turn away from people I care about	True	1
	Not true	0
I take good care of myself	True	0
	Not true	1
I am able to think about the future	True	0
	Not true	1
I just want to hide away	True	1
	Not true	0
I look forward to things	True	0
	Not true	1
I've forgotten what it's like to enjoy myself	True	1
	Not true	0

I can't be bothered with my friends	True	1
	Not true	0
I can cope easily with everyday tasks	True	0
	Not true	1
I cut myself off from other people	True	1
	Not true	0
It is difficult for me to make even simple decisions	True	1
	Not true	0
I feel as if I am a burden to people	True	1
	Not true	0
Most of the time I just sit and stare into space	True	1
	Not true	0
I can't face anyone	True	1
	Not true	0
I shut everything out	True	1
	Not true	0
I'm neglecting my appearance	True	1
	Not true	0
I can see the funny side of things	True	0
	Not true	1
I don't take in what people say to me	True	1
	Not true	0
I feel as if I'm letting everyone down	True	1
	Not true	0
I dread each coming day	True	1
	Not true	0
I enjoy my food	True	0
	Not true	1
I avoid people if I can	True	1
	Not true	0
I am reluctant to answer the door or the telephone	True	1
	Not true	0
My life has no meaning	True	1
	Not true	0
I am able to cope with everyday problems	True	0
	Not true	1

In case there are missing items, it is recommended that for respondents with between one and six missing responses (that is, cases with less than 20% missing data), the total score is calculated as follows:

$$T = x / (34 - m) * 34$$

where T is the final total score, x is the item summation score, m is the number of missing items. Cases with more than six missing responses cannot be allocated a total score.

Analysis Methods

See section 5.5.1 for the analysis of the QLDS total score.

5.5.10. European Quality of Life Group, 5-Dimension, 5-Level (EQ-5D-5L)

Definitions

The EQ-5D-5L is a validated standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It consists of the EQ-5D-5L descriptive system and a visual analogue scale (EQ-VAS).

The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each of the 5 dimensions is divided into 5 levels of perceived problems (level 1 = no problem, level 2 = slight problems, level 3 = moderate problems, level 4 = severe problems, level 5 = extreme problems). The participant selects an answer for each of the 5 dimensions considering the response that best matches his or her health "today." The descriptive system can be represented as a health state. Individual scores from the 5 dimensions will be used to obtain a weighted health status index as follows:

i) Scores from each dimension will be combined to obtain a 5L health state: e.g., a score of 1 for each dimension will give a 5L health state of 11111. Dimension scores will be combined in the following order: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression;

ii) The EuroQol Group coordinated a study that administered both the 3-level and 5-level versions of the EQ-5D, in order to develop a "crosswalk" between the EQ-5D-3L value sets and the new EQ-5D-5L descriptive system, resulting in crosswalk value sets for the EQ-5D-5L.
Interim Scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L Value Sets (Van Hout et al, 2012);

iii) The UK value set will be used to get the health utility values for all the countries participating in the study. See "*EQ-5D-5L_Crosswalk_Value_Sets.xls*".

The EQ-VAS self-rating records the respondent's own assessment of his or her overall health status at the time of completion, on a scale of 0 to 100.

Analysis Methods

See section 5.5.1 for the analysis of the EQ-Health-Utility and the EQ-VAS.

Frequency distributions will be provided for the 5 dimensions of the EQ-5D-5L descriptive system for each scheduled visit. Summaries of both observed and LOCF data will be presented.

5.5.11. 36-Item Short-Form Health Survey (SF-36v2)

Definitions

The SF-36 is a validated 36-item questionnaire which measures quality of life across 8 domains, which are both physically and emotionally based. Version 2 of this questionnaire, with a 4-week recall (standard version) will be used for this study. The 8 domains that the SF-36 measures are as follows: physical functioning; role limitations due to physical health; role limitations due to emotional problems; energy/fatigue; emotional wellbeing; social functioning; pain; general health. In addition to the 8 scales two summary scales are calculated, the physical component summary scale (PCS) and the mental component summary scale (MCS). A single item (item 2) is also included that identifies perceived change in health, "Compared to one year ago, how would you rate your health in general now?".

Individual items will be scored on a 3-point, 5-point or 6-point scale. To construct the 8 dimensions, items will be recoded, the item values will be summed and transformed to a score of 0 to 100, where 100 indicates the best possible answer and 0 the worst possible answer. Finally, a

norm-based score will be calculating. See the following table that defines the domains and the item recoding.

Dimension	Item	Abbreviated Item Content	Precoded	Final value
Physical Functioning (PF)	3a	Vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports	1, 2, 3	1, 2, 3
	3b	Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf		
	3c	Lifting or carrying groceries		
	3d	Climbing several flights of stairs		
	3e	Climbing one flight of stairs		
	3f	Bending, kneeling, or stooping		
	3g	Walking more than a mile		
	3h	Walking several hundred yards		
	3i	Walking one hundred yards		
	3j	Bathing or dressing oneself		
Role-Physical (RP)	4a	Cut down the amount of time one spent on work or other activities	1, 2, 3, 4, 5	1, 2, 3, 4, 5
	4b	Accomplished less than you would like		
	4c	Limited in kind of work or other activities		
	4d	Had difficulty performing work or other activities (e.g., it took extra effort)		
Bodily Pain (BP)	7	Intensity of bodily pain	1, 2, 3, 4, 5, 6	6.0, 5.4, 4.2, 3.1, 2.2, 1.0
	8	Extent pain interfered with normal work	If item 7 is not answered: 1, 2, 3, 4, 5	6.0, 4.75, 3.5, 2.25, 1.0
			If item 7 is answered as 1 and item 8 as 1	6
			If item 7 is answered as 2-6 and item 8 as 1	5
			If item 7 is answered as 1-6 and item 8 as: 2. 3. 4. 5	4. 3. 2. 1
General Health (GH)	1	Is your health: excellent, very good, good, fair, poor	1, 2, 3, 4, 5	5.0, 4.4, 3.4, 2.0, 1.0
	11a	Seem to get sick a little easier than other people	1, 2, 3, 4, 5	1, 2, 3, 4, 5
	11b	As healthy as anybody I know	1, 2, 3, 4, 5	5, 4, 3, 2, 1
	11c	Expect my health to get worse	1, 2, 3, 4, 5	1, 2, 3, 4, 5
	11d	Health is excellent	1, 2, 3, 4, 5	5, 4, 3, 2, 1
Vitality (VT)	9a	Feel full of life	1, 2, 3, 4, 5	5, 4, 3, 2, 1
	9e	Have a lot of energy	1, 2, 3, 4, 5	5, 4, 3, 2, 1
	9g	Feel worn out	1, 2, 3, 4, 5	1, 2, 3, 4, 5
	9i	Feel tired	1, 2, 3, 4, 5	1, 2, 3, 4, 5
Social Functioning (SF)	6	Extent health problems interfered with normal social activities	1, 2, 3, 4, 5	5, 4, 3, 2, 1
	10	Frequency health problems interfered with social	1, 2, 3, 4, 5	1, 2, 3, 4, 5
Role-Emotional (RE)	5a	Cut down the amount of time spent on work or other activities	1, 2, 3, 4, 5	1, 2, 3, 4, 5
	5b	Accomplished less than you would like		
	5c	Did work or other activities less carefully than usual		

Dimension	Item	Abbreviated Item Content	Precoded	Final value
Mental Health (MH)	9b 9c 9d 9f 9h	Been very nervous Felt so down in the dumps that nothing could cheer you up Felt calm and peaceful Felt downhearted and depressed	1, 2, 3, 4, 5 1, 2, 3, 4, 5 1, 2, 3, 4, 5 1, 2, 3, 4, 5 1, 2, 3, 4, 5	1, 2, 3, 4, 5 1, 2, 3, 4, 5 5, 4, 3, 2, 1 1, 2, 3, 4, 5 5, 4, 3, 2, 1
Reported	2	How health is now compared to 1 year ago	1, 2, 3, 4, 5	1, 2, 3, 4, 5
An excerpt from the User's Manual for the SF-36v2 Health Survey				

Each raw scale score will be transformed to a 0 – 100 scale using the formula shown below and using the information of the following table:

Scale	Lowest possible raw score	Possible raw score range
Physical Functioning (PF)	10	20
Role-Physical (RP)	4	16
Bodily Pain (BP)	2	10
General Health (GH)	5	20
Vitality (VT)	4	16
Social Functioning (SF)	2	8
Role-Emotional (RE)	3	12
Mental Health (MH)	5	20

If PF is the raw score for the Physical Functioning scale, then:

*PFtrans = 100 * (PF – "lowest possible raw score") / "possible raw score range"*

For ease of interpretation the domain scores are converted to norm-based scores with mean=50 and SD=10, using the formulas (given for Physical Functioning scale):

$PFz\text{-}score = (PFtrans - mean_{PF}) / SD_{PF}$

*Norm-based PF = PFz * 10 + 50*

The mean and SD to calculate the z-scores for the 8 scales are in the following table:

SF-36 scale	Mean	SD
PF	83.29094	23.75883
RP	82.50964	25.52028
BP	71.32527	23.66224
GH	70.84570	20.97821
VT	58.31411	20.01923
SF	84.30250	22.91921
RE	87.39733	21.43778
MH	74.98685	17.75604

(see: Ware JE, Kosinski M, Dewey JE. How to Score Version 2 of the SF-36® Health Survey. Lincoln, RI: QualityMetric Incorporated, 2000).

The physical component summary scale (PCS) and the mental component summary scale (MCS). are calculated as follows:

PCS = PFz * 0.42402 + RPz * 0.35119 + BPz * 0.31754 + GHz * 0.24954 +
VTz * 0.02877 + SFz * -0.00753 + REz * -0.19206 + MHz * -0.22069

MCS = PFz * -0.22999 + RPz * -0.12329 + BPz * -0.09731 + GHz * -0.01571 +
VTz * 0.23534 + SFz * 0.26876 + REz * 0.43407 + MHz * 0.48581

And then both scales will be converted to norm-based score in the same way as above.

Analysis Methods

See section 5.5.1 for the analysis of the norm-based scores of the 8 SF-36v2 dimensions and the two summary scores.

Frequency distributions will be provided for item 2 of the SF-36v2 for each scheduled visit. Summaries of both observed and LOCF data will be presented.

5.5.12. Sheehan Disability Scale (SDS)

Definitions

The SDS will be used to assess the secondary objective of functional impairment and associated disability. The SDS is a validated PRO measure consisting of a 5-item questionnaire that has been widely used and accepted for assessment of functional impairment and associated disability. The first 3 items assess disruption of (1) work/school, (2) social life, and (3) family life/home responsibilities using a rating scale from 0 to 10. The SDS also has 1 item assessing days lost from school or work and 1 item assessing days of underproductivity. The recall period for this study is 7 days. The first item (work/school) may be missing due to not working/studying unrelated to the disease.

The scores for the first 3 items are summed to create a total score of 0 to 30, where higher score indicates greater impairment. Scores ≤ 2 for each item and ≤ 6 for the total score are considered functional remission. If one of the first three items is missing, the total score will be calculated by imputing the missing item with the average of the other two items. Otherwise the total score will be set to missing as well as remission status.

Analysis Methods

See section 5.5.1 for the analysis of the SDS total score and the days lost items.

Frequency distributions will be provided for the SDS remission for each scheduled visit. Summaries of both observed and LOCF data will be presented.

5.5.13. Work Productivity and Activity Impairment (WPAI-D)

Definitions

The WPAI:D questionnaire is a validated short instrument that assesses impairment in work and other regular activities over the past 7 days. The WPAI yields four types of scores:

1. Absenteeism (work time missed)
2. Presenteeism (impairment at work / reduced on-the-job effectiveness)

3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)
4. Activity Impairment.

The first three scores will be derived only for respondents who are working (should be missing for non-working), but the last score is applicable for all respondents. WPAI scores are expressed as percent impairment, with higher values indicating greater impairment. A score cannot be calculated if there is a missing response to the corresponding item.

The questions of the WPAI-D are:

Q1 = currently employed

Q2 = hours missed due to problems associated with depression

Q3 = hours missed other reasons

Q4 = hours actually worked

Q5 = degree depression affected productivity while working

Q6 = degree depression affected regular activities

The 4 scores are calculated as follows:

1. Absenteeism: Q2*100/(Q2+Q4)
2. Presenteeism: Q5*10
3. Work productivity loss: 100*[Q2/(Q2+Q4) + (1 - Q2/(Q2+Q4)) * Q5/10]
4. Activity Impairment: Q6*10

Analysis Methods

See section 5.5.1 for the analysis of the 4 WPAI scores.

5.6. Tertiary/Exploratory Endpoint(s) Analysis

Not applicable.

5.7. (Other) Safety Analyses

All safety analyses will be based on the safety analysis set (based on actual intervention received), unless otherwise specified.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.7.1. Extent of Exposure

The number and percentage of participants who receive each study agent within a study intervention will be summarized.

Descriptive statistics for duration of study intervention (N, mean, SD, median, and range (minimum, maximum)) will be summarized.

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) +1.

A frequency distribution of the total number of dosing sessions of intranasal study medication will be presented.

Starting dose for a participant is defined as the first dose taken after randomization. Modal dose for a participant is defined as the most frequently taken dose by a participant. Mean dose of a participant is calculated as the sum of doses during the phase divided by the total number of days exposed in the phase. The final dose is the last non-zero dose received during the phase. The calculation of mean, modal and final dose will exclude days off study drug.

Descriptive statistics (N, mean, SD, median, minimum and maximum) of starting dose, modal dose, mean dose and final dose will be presented for quetiapine XR and oral AD. For esketamine a frequency distribution will be presented.

The number (%) of participants with a dose adjustment/dose not administered will be summarized for each study agent within a study intervention. Reasons for dose adjustments/doses not administered will also be summarized.

5.7.2. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's 2-week safety follow-up visit. Serious AEs, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported.

Any AE occurring at or after the initial administration of study intervention through completion of the participant's 2-week safety follow-up visit is considered to be treatment emergent. Serious AEs reported within 30 days after the last dose of study intervention are also regarded as treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summary tables, for the first 8 weeks and for the whole study, will be provided for treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of each study agent within a study intervention
- AEs by severity

- AEs by relationship to each study agent within a study intervention
- AEs leading to dose interruption/dose modification of each study agent within a study intervention.

In addition to the summary tables, listings will be provided for participants who:

- Had SAEs
- Had AEs leading to discontinuation of study intervention.

Incidence of treatment-emergent adverse events of special interest will be summarized, grouped in the following MedDRA-based categories: sedation, dissociation, suicidality, suggestive of abuse potential, cystitis, and hepatic impairment. See Appendix 8 for a list of adverse events in each category.

The number and percentage of participants taking concomitant medication for dissociation events (preferred term of Dissociation) at any time during each treatment phase will be provided.

A listing of participants who died will be provided.

5.7.3. Additional Safety Assessments

5.7.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics (N, mean, SD, median and range) for observed values and changes from baseline will be provided for clinical laboratory tests (hematology, chemistry, and urinalysis) at each scheduled time point by intervention group.

Clinical laboratory tests that meet the criteria for markedly abnormal will be listed by participant for each phase. The incidence of treatment-emergent markedly abnormal laboratory values that occurred at any time during the treatment phase will be presented. Clinical laboratory test values will be considered treatment-emergent markedly abnormal (TEMA) using the criteria defined by the sponsor listed in Attachment 10. The identification of TEMA laboratory values is based on the post-baseline value being out of range while the baseline value is either missing or within the range given in Attachment 10. If post-baseline laboratory results are above the upper limit and the baseline value is below the lower limit, then the post-baseline abnormality will also be considered TEMA. The same applies to the post-baseline value being below the lower limit with the baseline value being above the upper limit.

The incidence of participants with ALT or AST values > 3*upper normal limit (ULN) will be presented. Additionally, incidence of hepatic toxicity (Hy's Law) defined as ALT or AST values > 3*ULN AND total bilirubin values > 2*ULN will be presented. Similar to the markedly abnormal analysis, only participants with baseline ALT or AST values ≤ 3*ULN (AND baseline total bilirubin values ≤ 2*ULN for hepatic toxicity) (or if the baseline value is missing) will be eligible for these analyses.

5.7.3.2. Vital Signs and Physical Examination Findings

Vital sign parameters weight, pulse, blood pressure (systolic and diastolic) and respiratory rate will be summarized at each assessment time point, including the change from baseline, will be summarized by intervention group.

In addition, descriptive statistics of pre-dose and post-dose pulse rate, blood pressure (systolic and diastolic) values and respiratory rate, and changes from pre-dose will be provided for each intranasal dosing day.

Abnormality criteria (based on criteria defined in the table below) will be applied to baseline and postbaseline values. For baseline values, increase or decrease criteria are not applied.

Postbaseline values will be considered TE if they meet both value and change criteria in the table below.

For criteria that do not include an increase or decrease from baseline:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (eg, Normal or High).
- If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

Incidence of treatment-emergent abnormal vital signs during intervention, as defined in the table below, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign.

Table: Treatment-Emergent Abnormality Categories for Vital Signs

	Post-baseline value outside of normal limit if:	
Vital Parameter	Abnormally low	Abnormally high
Pulse (bpm)	A decrease from Baseline of ≥ 15 to a value ≤ 50	An increase from Baseline of ≥ 15 to a value ≥ 100
Systolic BP (mmHg)	A decrease from Baseline of ≥ 20 to a value ≤ 90	An increase from Baseline of ≥ 20 to a value ≥ 180
Diastolic BP (mmHg)	A decrease from Baseline of ≥ 15 to a value ≤ 50	An increase from Baseline of ≥ 15 to a value ≥ 105
Respiratory rate (breaths per minute)	Any value < 10	Any value > 24

BP = blood pressure; Baseline is defined in Section **Error! Reference source not found.**.

The proportion of subjects who experienced treatment-emergent acute hypertension (systolic BP ≥ 180 or diastolic BP ≥ 110) at any time during each treatment phase will be summarized.

5.7.3.3. Electrocardiogram

For the scheduled time points the following items will be summarized:

- Was the ECG performed, Yes / No;
- Overall interpretation, Normal / Abnormal / Not evaluable;
- Clinically significant, Yes / No.

In case the interpretation is abnormal, the specification will be listed.

In case the abnormality is assessed to be clinically significant, the associated Medical History Condition and/or Adverse Event will be listed.

5.7.3.4. Nasal Examination

During the predose nasal examination the grade of the symptoms epistaxis, nasal crusts, nasal discharge and nasal erythema, scored as absent, mild, moderate or severe, will be summarized as frequency distributions. Comments to the symptom assessments will be listed.

5.7.3.5. Pregnancy testing

The results of the pregnancy test (positive, negative, borderline, invalid) will be summarized at each scheduled time point as frequency distributions.

5.7.3.6. Columbia–Suicide Severity Rating Scale

The Columbia–Suicide Severity Rating Scale (C-SSRS) is an assessment tool that evaluates suicidal ideation and behavior. The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the composite and comparative endpoints, and to enable clarity in the presentation of the results:

Suicidal Ideation	Category 1	Wish to be dead
	Category 2	Non-specific active suicidal thoughts
	Category 3	Active suicidal ideation with any methods (not plan) without intent to act
	Category 4	Active suicidal ideation with some intent to act, without specific plan
	Category 5	Active suicidal ideation with specific plan and intent
Suicidal behavior	Category 6	Preparatory acts or behavior
	Category 7	Aborted attempt
	Category 8	Interrupted attempt
	Category 9	Actual attempt (non-fatal)
	Category 10	Completed suicide

Non-suicidal self-injurious behavior is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below:

- *Suicidal ideation*: A “yes” answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- *Suicidal behavior*: A “yes” answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.

- *Suicidal ideation or behavior*: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

The following outcome is a numerical score derived from the C-SSRS categories. The score is created at each assessment for each patient.

Suicidal ideation score: The maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.

Note that missing data should not be imputed.

The incidence of the 11 items (the 10 categories and the 'Non-suicidal self-injurious behavior') and the 3 composite endpoints will be summarized as frequency distributions at screening and/or baseline (combined), and at any of the assessments during treatment (worst score during treatment).

The maximum score (from the 10 categories) assigned for each subject will also be summarized into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1 - 5), Suicidal behavior (6 - 10). Shifts from the screening/baseline value to the maximum category during treatment will be summarized as frequency distributions.

For the suicidal ideation score the shift from screening/baseline to the maximum during treatment will be summarized as frequency distributions.

5.7.3.7. Other Safety Parameters

Not applicable

5.8. Other Analyses

5.8.1. Pharmacokinetics

Not applicable

5.8.2. Immunogenicity

Not applicable

5.8.3. Pharmacodynamics

Not applicable

5.8.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable

5.8.5. Biomarkers

Details of the analysis plan and summary of results from both biomarker and pharmacogenomic analyses will be reported separately.

5.8.6. Health Economics

Not applicable

5.8.7. Definition of Subgroups

The following subgroups will be used to summarize parameters:

Subgroup	Variant	Definition
Sex	1	• Male • Female
Age Group	1	• Adult [18-64] • Elderly [>=65]
Number of previous treatment failures	1	• 2 • >=3
Class of continued oral AD	1	• SNRI • SSRI

The following parameters will be analyzed as described in the respective sections for the subgroups:

- Selected demographic and disease characteristics;
- The primary parameter and the major secondary parameter;
- MADRS;
- CGI-S and CGI-C;
- PHQ-9;
- QLDS;
- Selected AE parameters (including AEs of special interest).

5.9. Interim Analyses

Not applicable.

5.10. Follow-up Phase

The follow-up phase starts when a randomized participant discontinues study intervention. The starting visit of the follow-up phase is the visit when the treatment discontinuation occurs, or the visit closest to the treatment discontinuation. The follow-up analysis set will be used for all analyses. Analyses will be presenting observed data only and uses descriptive methods. For continuous parameters the change from starting visit of the follow-up phase will also be summarized. Data will be presented by group where to participant was randomized to and overall.

The following parameters will be analyzed as described in the respective sections:

- Selected demographic and disease characteristics;
- Treatment administered;
- Remission and relapse;
- MADRS;
- CGI-S;

- PHQ-9;
- QLDS;
- (Serious) Adverse events recorded during a Janssen treatment for depression.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	adverse event
ALT/SGPT	alanine aminotransferase
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IWRS	interactive web response system
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardized MedDRA queries
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

The analysis of time to event endpoints as described in the protocol includes both descriptive analysis, log-rank test and Cox proportional hazards model. However, since time to relapse is an exploratory endpoint, the analysis of this endpoint will only be descriptive.

6.3. Appendix 3 Demographics and Baseline Characteristics

6.3.1. Demographics

The following demographic variables will be summarized by intervention group:

Continuous Variables	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]
Weight (kg) at baseline	
Categorical Variables	
Age (18-64 years, >=65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, undifferentiated)	
Japanese Ancestry (Yes, No)	
Occupational/employment status (full time employed, part time employed, casually employed, sheltered work, employed, but currently on sick or disability leave, unemployed due to depression, but seeking work, unemployed for reasons unrelated to depression, but seeking work, unemployed due to depression, but not seeking work, unemployed for reasons unrelated to depression, but not seeking work, retired, housewife or dependent husband/partner, student, no information available)	

The following variables will be summarized for female participants by intervention group:

Continuous Variables	**Summary Type**
Average length of menstrual cycle (days)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]
Time from last menstrual period to date of assessment	
Categorical Variables	
Subject's childbearing potential (of childbearing potential, permanently sterilized, postmenopausal, not applicable)	Frequency distribution with the number and percentage of participants in each category.
Did menstrual period occur since last assessment (Yes, No)	

6.3.2. Nasal examination

The following variables will be summarized for the nasal examination performed at screening by intervention group:

Categorical Variables	**Summary Type**
Condition (Structural/Functional Abnormalities, Septal Deviation, Signs of Infections, Obstruction/Functional Lesions, Other Findings)	Frequency distribution with the number and percentage of participants in each category.

The specifications of the conditions recorded will be listed.

6.3.3. Psychiatric history

The following variables will be summarized for the psychiatric history performed at screening by intervention group:

Continuous Variables	**Summary Type**
Subjects age in years when diagnosed with MDD (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]
Total number of major depressive episodes to date, including current episode	
Duration of Current Episode (weeks)	
Categorical Variables	
Would the subject be eligible for electroconvulsive therapy, had he/she NOT been enrolled in this clinical trial (Yes, No)	Frequency distribution with the number and percentage of participants in each category.
Does the subject have a family history of psychiatric disorders (Yes, No, Unknown)	
Psychiatric Disorder (Alcohol Abuse, Anxiety Disorder, Bipolar Disorder, Depression, Schizophrenia, Substance, Abuse, Other)	
Check all family members who have or had the selected psychiatric disorder (Father, Mother, Siblings, Other)	

The specified Other psychiatric disorders and Family members will be listed.

6.3.4. Mini International Neuropsychiatric Interview (MINI)

Participants will undergo the MINI (a structured diagnostic interview) to confirm the diagnosis of MDD and to determine if there are other psychiatric conditions present.

The following variables will be summarized for the MINI performed at screening by intervention group:

Categorical Variables	**Summary Type**
Was the questionnaire completed (Yes, No)	Frequency distribution with the number and percentage of participants in each category.
Reason Not Done (Subject too ill, Subject refused, Other)	
Major depressive episode, Current (2 weeks)	
Major depressive episode, Past	
Major depressive episode, Recurrent	
Major depressive disorder, Current (2 weeks)	
Major depressive disorder, Past	
Major depressive disorder, Recurrent	
Suicidality, Current (Past Month)	
Suicidality, Lifetime attempt	
Suicidality level (Low, Moderate, High)	

Suicide behavior disorder, Current	
Suicide behavior disorder, In early remission	
Manic episode, Current	
Manic episode, Past	
Hypomanic episode, Current	
Hypomanic episode, Past	
Hypomanic episode, Not Explored	
Bipolar I disorder, Current	
Bipolar I disorder, Past	
Bipolar I disorder with psychotic features, Current	
Bipolar I disorder with psychotic features, Past	
Bipolar II disorder, Current	
Bipolar II disorder, Past	
Other specified bipolar and related disorder, Current	
Other specified bipolar and related disorder, Past	
Panic disorder, Current (Past Month)	
Panic disorder, Lifetime	
Agoraphobia, Current	
Social anxiety disorder (Social Phobia), Current (Past Month)	
Obsessive-compulsive disorder, Current (Past Month)	
Posttraumatic stress disorder, Current (Past Month)	
Alcohol use disorder, Past 12 Months	
Substance use disorder (Non-alcohol), Past 12 Months	
Any psychotic disorder, Current	
Any psychotic disorder, Lifetime	
Major depressive disorder with psychotic features, Current	
Major depressive disorder with psychotic features, Past	
Bipolar I disorder with psychotic features, Current	
Bipolar I disorder with psychotic features, Past	
Anorexia nervosa, Current (Past 3 Months)	
Bulimia nervosa, Current (Past 3 Months)	
Binge-eating disorder, Current (Past 3 Months)	
Generalized anxiety disorder, Current (Past 6 Months)	
Medical, organic, drug cause ruled out (No, Yes, Uncertain)	
Antisocial personality disorder, Lifetime	
Primary diagnosis (Major depressive episode, …)	

The specified Other reasons for MINI not done will be listed.

6.3.5. Inventory of Depressive Symptomatology (Clinician-Rated)

The 30 item Inventory of Depressive Symptomatology clinician rated (IDS-C30) is designed to assess the severity of depressive symptoms. Each item is interval scaled from 0 to 3; 0 indicates absence of the symptom during the last 7 days. The IDS-C30 is scored by summing responses to 28 of the 30 items to obtain a total score ranging from 0 to 84. Either appetite increase or decrease, but not both, are used to calculate the total score. Weight increase or decrease, but not both, are used to calculate the total score.

The following variables will be summarized for the IDS-C30 performed at screening by intervention group:

Continuous Variables	**Summary Type**
IDS-C30 total score	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]
Categorical Variables	
Was the questionnaire completed (Yes, No)	Frequency distribution with the number and percentage of participants in each category.
Reason Not Done (Subject too ill, Subject refused, Other)	

The specified Other reasons for IDC-C30 not done will be listed.

6.3.6. Psychotherapy

The following variables will be summarized for the investigator discussion with the participant regarding psychotherapy by intervention group:

Categorical Variables	**Summary Type**
Discussion of initiation/continuation of psychotherapy during study has taken place prior to randomization (Yes, No)	Frequency distribution with the number and percentage of participants in each category.
Psychotherapy recommended based on pre-randomization discussion (Yes, No)	
Decision by the participant to follow the recommendation (prior to randomization) (Decision to follow recommendation, Decision to not follow recommendation)	
Psychotherapy started (Yes, No)	
Category of started psychotherapy (Cognitive–behavioral therapy, Nondirective supportive therapy, Behavioral activation therapy, Psychodynamic therapy, Systemic therapy, Problem-solving therapy, Interpersonal psychotherapy, Social skills training, Other)	
Reason for starting (Patient's wish/preference, Suggested by treating physician, Suggested by third party, Unspecified - started prior the study, Other)	
Frequency (once, infrequent, as necessary, continue, daily, twice daily, three times daily, four times daily, every other day, weekly, twice weekly, three times weekly, four times	

weekly, every two weeks, every four weeks, monthly, twice per month, every three months, thrice, unknown, other)	
Reason for stopping (Patient's decision, Lack of efficacy, Lack of tolerability, Lack of cooperation, Other)	
Reason for change to another psychotherapeutic intervention (Suggested by the therapist, Lack of efficacy, Lack of tolerability, Lack of cooperation, Other)	
Participant´s adherence to psychotherapeutic intervention (Good, Moderate, Bad)	

The other specifications for psychotherapy, reason for starting, reason for stopping and reason for change to another psychotherapeutic intervention will be listed.

6.3.7. Urine screen for drugs of abuse

The following variables will be summarized for the Urine screen for drugs of abuse performed at screening by intervention group:

Categorical Variables	**Summary Type**
Was the sample collected (Yes, No)	Frequency distribution with the number and percentage of participants in each category.
Amphetamine (Positive, Negative)	
Barbiturate (Positive, Negative)	
Cannabinoids (Positive, Negative)	
Cocaine (Positive, Negative)	
Methadone (Positive, Negative)	
Methamphetamine (Positive, Negative)	
Opiate (Positive, Negative)	
Phencyclidine (Positive, Negative)	

6.3.8. Preplanned surgeries/procedures

The following variables will be summarized for preplanned surgeries/procedures by intervention group:

Categorical Variables	**Summary Type**
Are there any planned/scheduled surgeries/procedures which require hospitalization during the course of this trial (Yes, No)	Frequency distribution with the number and percentage of participants in each category.
Allergic/Immunologic (ongoing yes / no)	
Cardiovascular (ongoing yes / no)	
Dermatologic (ongoing yes / no)	
Ears, Nose and Throat/ (ongoing yes / no)	
Endocrine and Metabolic (ongoing yes / no)	
Eyes (ongoing yes / no)	

Gastrointestinal (ongoing yes / no)	
Genito-urinary (ongoing yes / no)	
Hematopoietic/Lymphatic (ongoing yes / no)	
Musculoskeletal (ongoing yes / no)	
Neurologic (ongoing yes / no)	
Psychiatric (ongoing yes / no)	
Reproductive/Breast (ongoing yes / no)	
Respiratory (ongoing yes / no)	
Other (ongoing yes / no)	
Indication (Medical History, Prophylaxis, Other)	

Details of surgery/procedure and associated medical history/prophylaxis/other will be listed.

6.4. Appendix 4 Major Protocol Deviations

In general, major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock. See the study specific Major Protocol Deviation Criteria document.

The participants with major protocol deviations will be summarized by category ("Protocol Deviation Coded Term)". Major protocol deviations will be listed presenting the coded term and the description ("PD criterion").

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC term and study intervention. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. In addition, concomitant medications of special interest will be presented as administered before the study intervention and during the study. These include benzodiazepines and sleeping medications. See Appendix 9 for specifications of the medications.

The indication of the concomitant medications will be summarized by study intervention. The associated adverse events or medical histories will be summarized.

Note: the SSRI/SNRI continued during the study in combination with the study drug is summarized separately. See section 5.7.1.

Prior medications, meaning the retrospective treatment failures, will be summarized by substance class, substance name and study intervention. The number of treatment failures will be summarized by study intervention.

6.6. Appendix 6 Medical History

The following variables will be summarized for subjects who experienced any past and/ or concomitant diseases at screening by intervention group:

Categorical Variables	**Summary Type**
Allergic/Immunologic (ongoing yes / no)	Frequency distribution with the number and percentage of participants in each category.
Cardiovascular (ongoing yes / no)	
Dermatologic (ongoing yes / no)	
Ears, Nose and Throat/ (ongoing yes / no)	
Endocrine and Metabolic (ongoing yes / no)	
Eyes (ongoing yes / no)	
Gastrointestinal (ongoing yes / no)	
Genito-urinary (ongoing yes / no)	
Hematopoietic/Lymphatic (ongoing yes / no)	
Musculoskeletal (ongoing yes / no)	
Neurologic (ongoing yes / no)	
Psychiatric (ongoing yes / no)	
Reproductive/Breast (ongoing yes / no)	
Respiratory (ongoing yes / no)	
Other (ongoing yes / no)	

The verbatim term for the medical history condition/event will be listed.

6.7. Appendix 7 Intervention Compliance

Compliance calculation is not applicable for this study.

Relevant deviations from the dosing schedules will be documented through major protocol deviations. See the Major Protocol Deviation Criteria document for this study.

6.8. Appendix 8 Adverse Events of Special Interest

Adverse events of special interest are defined and grouped in the following MedDRA based categories as follows:

Sedation: sedation; somnolence; altered state of consciousness; depressed level of consciousness; hypersomnia; stupor

Dissociation: depersonalisation/derealisation disorder; derealisation; dissociative disorder; flashback; hallucination; hallucination, auditory; hallucination, visual; hallucination, illusion; somatic hallucination; hyperacusis; tinnitus; diplopia; vision blurred; ocular discomfort; photophobia; visual impairment; dysesthesia; oral dysesthesia; paraesthesia; paraesthesia oral; pharyngeal paraesthesia; time perception altered; daydreaming; delusional perception; feeling hot; feeling cold; feeling of body temperature change

Suicidality: completed suicide; depression suicidal; intentional overdose; intentional self-injury; multiple drug overdose intentional; poisoning deliberate; self-injurious behavior; self-injurious ideation; suicidal behavior; suicidal ideation; suicide attempt; toxicity to various agents

Suggestive of abuse potential: aggression; confusional state; decreased activity; dependence; disorientation; dissociation; dissociative disorder; dizziness; drug abuse; drug abuser; drug dependence; drug use disorder; drug detoxification; drug diversion; drug rehabilitation; drug tolerance; drug tolerance increased; drug withdrawal convulsions; drug withdrawal headache; drug withdrawal syndrome; euphoric mood; feeling abnormal; feeling drunk; feeling of relaxation; hallucination; hallucination, auditory; hallucination, gustatory; hallucination, olfactory; hallucination, synesthetic; hallucination, tactile; hallucination, visual; hallucinations, mixed; inappropriate affect; mental impairment; product tampering; psychomotor hyperactivity; psychotic disorder; rebound effect; somatic hallucination; somnolence; substance abuser; substance dependence; substance use; substance use disorder; substance-induced mood disorder; substance-induced psychotic disorder; thinking abnormal; withdrawal arrhythmia; withdrawal syndrome

Cystitis: allergic cystitis; chemical cystitis; cystitis; cystitis erosive; cystitis hemorrhagic; cystitis interstitial; cystitis noninfective; cystitis ulcer active; cystitis-like symptom; pollakiuria; dysuria; micturition urgency; nocturia

Hepatic impairment: cholestasis and jaundice of hepatic origin; hepatic failure; fibrosis and cirrhosis; other liver damage-related conditions

6.9. Appendix 9 Medications of Special Interest

Concomitant medications of special interest are defined as follows:

Concomitant Medication Special Interest Category	**Selection**	**Note**
benzodiazepines	ATC level 3 class name ANXIOLYTICS	ATC level 3 code N05B
benzodiazepines	ATC level 3 class name HYPNOTICS AND SEDATIVES	ATC level 3 code N05C
sleep medication	quetiapine	Low dose, daily dose ≤ 50 mg

6.10. Appendix 10 Criteria of Markedly Abnormal Laboratory Values

	Markedly Abnormal Limits	
Laboratory Parameter	**Low**	**High**
Alanine aminotransferase (ALT) (SGPT) [U/L]	N/A	200
Alanine aminotransferase (ALT) (SGPT) [U/L]	N/A	>3X ULN
Albumin [g/L]	24	60
Alkaline phosphatase [U/L]	N/A	250
Aspartate aminotransferase (AST) (SGOT) [U/L]	N/A	250
Aspartate aminotransferase (AST) (SGOT) [U/L]		>3X ULN
Basophils [%]	N/A	6
Bicarbonate [mmol/L]	15.1	34.9
Bilirubin, total [µmol/L]	N/A	51.3
Blood urea nitrogen [mmol/L]	N/A	17.9
Calcium [mmol/L]	1.5	3
Chloride [mmol/L]	94	112
Creatine kinase (U/L)	N/A	990
Creatinine [µmol/L]	N/A	265.2
Eosinophils [%]	N/A	10
Erythrocytes (RBC) [x1012/L] -- female	3.0	5.5
-- male	3.0	6.4
Gamma glutamyl transferase [U/L]	N/A	300
Glucose [mmol/L]	2.2	16.7
Hemoglobin [g/L]	80	190
Hematocrit [fraction] -- female	0.28	0.50
-- male	0.24	0.55
Lactate Dehydrogenase [U/L]	N/A	500
Leukocytes (WBC) [x109/L]	2.5	15.0
Lymphocytes [%]	10	60
Monocytes [%]	N/A	20
Neutrophils, segmented [%]	30	90
Phosphate [mmol/L]	0.7	2.6
Platelet count [x109/L]	100	600
Potassium [mmol/L]	3.0	5.8
Protein, total [g/L]	50	N/A
Sodium [mmol/L]	125	155
Urate [µmol/L]	89.2	594.8
Urine pH	N/A	8.0
Hy's Law criteria:		
Alanine aminotransferase (ALT) (SGPT) [U/L] or Aspartate aminotransferase (AST) (SGOT) [U/L]		>3X ULN
AND		
Bilirubin, total [µmol/L]		>2X ULN

Note: The same limits apply to both males and females unless gender is indicated;
N/A = Not applicable.

7. REFERENCES