Janssen Research & Development

Statistical Analysis Plan

Open-label Long-Term Extension Study for Participants With Treatment-Resistant Major Depressive Disorder Who are Continuing Esketamine Nasal Spray Treatment From Study 54135419TRD3013

Protocol 54135419TRD4010; Phase 4

JNJ-54135419 (esketamine)

Status:	Approved
Date:	9 September 2024
Prepared by:	PPD Janssen Research & Development
Document No.:	EDMS-RIM-633020, 2.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

TABLE OF CONTENTS

VERSION HISTORY

Table 01:– SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	10 January 2022	Not Applicable	Initial release
2	9 September 2024	Change of window in definition of relapse	Protocol amendment
		Secondary endpoint regarding relapse will be based on subgroup of patients in remission at Week 8 of Study 54135419TRD3013	Clinical relevance
		Time to relapse	Alignment with 54135419TRD3013 SAP
		Removal of MMRM	Not needed (alignment with other long-term studies)
		Removal of Intervention Compliance	Not applicable for this study (alignment with 54135419TRD3013 SAP)
		Addition of more details of analyses	Clarification
		AE analysis	Additional analysis of AEs

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 Clinical Study Report for protocol 54135419TRD4010. Additional (abbreviated) SAPs may be developed for various supplementary and post-hoc analyses.

1.1. Objectives and Endpoints

Primary objective

The primary objective of this study is to assess the long-term safety and tolerability of esketamine nasal spray in combination with an SSRI/SNRI in participants who have completed 32 weeks of esketamine nasal spray treatment in Study 54135419TRD3013.

Secondary objectives

- To assess the long-term efficacy of esketamine nasal spray in combination with an SSRI/SNRI based on the proportion of participants being relapse-free at Week 104 (or end-of-study).

  A relapse is defined by any of the following:
  a) Worsening of depressive symptoms as indicated by Montgomery-Asberg Depression Rating Scale (MADRS) total score ≥22 confirmed by 1 additional assessment of MADRS total score ≥22 within the next 5 to 31 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.

- To assess the effect of esketamine nasal spray in combination with an SSRI/SNRI on:
  - Clinician-rated overall severity of depressive illness
  - Participant-reported depressive symptoms
  - Participant-reported health-related quality of life and health status

Exploratory objective

To assess the impact of switching the oral antidepressant (AD) with another compound from the SSRI/SNRI classes, in cases where the oral AD is switched due to tolerability.

1.2. Study Design

Study design and patient selection

This study is a single-arm, 2-year open-label extension to Study 54135419TRD3013 (ESCAPE-TRD study). The study 54135419TRD3013, was an open-label, randomized, active-controlled study to evaluate the efficacy, safety, and tolerability of flexibly dosed esketamine nasal spray compared with quetiapine extended release, both in combination with a continuing SSRI/SNRI, in participants 18 to 74 years of age, inclusive, with treatment-resistant Major Depressive Disorder. 676 participants were randomized in Study 54135419TRD3013 (ESCAPE-TRD) to receive either esketamine (N=336) or quetiapine (N=340) [CSR 54135419TRD3013 2023]. Participants who were randomly assigned to the esketamine arm in Study 54135419TRD3013 (ESCAPE-TRD study), up to N=336, , had esketamine nasal spray administered through Week 30 (every 2 week dosing) or Week 31 (once weekly dosing), completed the maintenance phase at Week 32, continue to benefit from esketamine nasal spray in combination with a continuing SSRI/SNRI in the opinion of the investigator, and commercial esketamine nasal spray is not accessible to them in their country, are eligible to enter this open-label extension study (Study 54135419TRD4010). At any point during the long-term extension study, participants who, in the opinion of the investigator, are no longer benefiting from treatment with esketamine nasal spray in combination with an SSRI/SNRI should be discontinued from the study; these participants will complete the early study withdrawal visit and then return for the safety follow-up visit 2 weeks (±2 days) after their last dose of esketamine nasal spray, unless they withdraw consent, are lost to follow-up, or have died.

Study participation will continue for up to a maximum of 2 years (104 weeks), or until esketamine nasal spray becomes accessible in the participant's local country, whichever occurs first. Participants will have access to esketamine nasal spray for a maximum of 2 years during this study. If esketamine nasal spray becomes accessible locally before the 2-year endpoint, then participants will be considered as having completed the open-label extension study and will be switched to a commercially available supply if in the opinion of the treating physician, the participant continues to benefit from treatment and the participant wishes to continue the esketamine nasal spray treatment. Once esketamine nasal spray becomes accessible in a given country, all participants in the long-term extension study will be discontinued at all sites in that country. Study site personnel will notify participants of study termination and schedule an end-of-study visit with each participant.

Randomization

Since this is an open-label extension to Study 54135419TRD3013, no randomization is performed.

Informed consent may be obtained from participants at any time in the 4 weeks before Day 1 (ie, at or after Week 28 visit in Study 54135419TRD3013). Day 1 of this study will be the day of the first esketamine nasal spray dose or Day 1 will be the date of informed consent.

Treatment exposure

It is the investigator's responsibility to contact the sponsor to request esketamine nasal spray supply for participants who will enroll in the long-term extension study. On Day 1 (Week 32 visit of Study 54135419TRD3013), participants who consented and are eligible will enter the 2-year open-label extension study. The dosage of esketamine nasal spray in this long-term extension study will be determined based on the participant's dose and frequency at completion of the maintenance phase (Week 32) of Study 54135419TRD3013. Investigators will be allowed to change the dose and frequency during the open-label extension study based on clinical judgment. Participants will attend site visits once weekly or every 2 weeks, depending on their dosing frequency, for administration of esketamine nasal spray. The SSRI/SNRI dose should have been optimized up to the maximum tolerated dose during Study 54135419TRD3013 as per the respective Summary of Product Characteristics (or local equivalent, if applicable). During the long-term extension study, a stable dose should be maintained; however, dose modifications to the continuing SSRI/SNRI may be made, if necessary, at the investigator's discretion. Additionally, during the long-term extension study, the SSRI/SNRI may be changed for individual participants by the investigator for tolerability issues. If the SSRI/SNRI is discontinued at any time during the study, the esketamine nasal spray must also be discontinued and the participant will be withdrawn from the study.

2. STATISTICAL HYPOTHESES

Due to the design of the study (single-arm, long-term extension) and the objective (exploratory nature) no formal statistical hypothesis is described for this study.

3. SAMPLE SIZE DETERMINATION

As no formal statistical hypothesis is specified for this study, no sample size estimation is performed. However, this is an extension part from the previous Study 54135419TRD3013 (ESCAPE-TRD), in which, 676 participants were randomized in to receive either esketamine (N=336) or quetiapine (N=340). Participants who were randomly assigned to the esketamine arm in Study 54135419TRD3013 (ESCAPE-TRD study), up to N=336 and who had esketamine nasal spray administered through Week 30 (every 2 week dosing) or Week 31 (once weekly dosing), completed the maintenance phase at Week 32, continue to benefit from esketamine nasal spray in combination with a continuing SSRI/SNRI in the opinion of the investigator, and commercial esketamine nasal spray is not accessible to them in their country, could be enrolled in this extension study. Therefore it is expected that from 100 to 200 participants will be enrolled.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	**Description**
Enrolled	All participants who sign the ICF
Safety/Efficacy	All participants who received at least 1 dose of esketamine anytime during the 54135419TRD4010 study.

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 to analysis visits.The visit windows and the target days for each visit are listed in Visit_windows_v2.xlsx. The reference day is Study Day 1, which is the day on which the patient receives the first dose of esketamine nasal spray in Study 54135419TRD4010. Study Day 1 should be within 14 days of the Study 54135419TRD3013 Week 32 visit date. 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 protocol 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. All data will be analysed and mapped into the visit windows. 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.

The number of participants for whom the Study 54135419TRD4010 Day 1 visit is later than the Study 54135419TRD3013 Week 32 visit will be presented. The number of days from the Study 54135419TRD3013 Week 32 visit to the Study 54135419TRD4010 Day 1 visit will be summarized.

For time-to-event analyses, the exact visit dates will be used to calculate the time to event.

5.2. Participant Dispositions

The number of screened participants and reasons for screen failure will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study:

- Participants enrolled
- Participants who received study intervention
- Participants who completed, terminated and reasons for termination from the study: if the reason for trial discontinuation is Withdrawal by Subject, the specific reason will also be summarized.

A participant will be considered to have completed the study if he or she has completed assessments at Week 104, or is discontinued from the study and completes end-of-study assessments when commercial esketamine nasal spray becomes accessible in the participant's local country and the study is terminated in the local country.

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

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

5.3. Primary Endpoint(s) Analysis

The primary analysis will be based on the Efficacy analysis set which will be same as Safety analysis set (due to design of the study) using the safety data collected during both Study 54135419TRD3013 and Study 54135419TRD4010.

5.3.1. Definition

The two primary endpoints are treatment-emergent adverse events, and Suicidal ideation and behavior: Columbia-Suicide Severity Rating Scale (C-SSRS).

Note: although the protocol lists intervention-emergent adverse events as a primary endpoint, here the terminology treatment-emergent adverse events will be applied.

5.3.2. Estimand for treatment-emergent adverse events

Primary Trial Objective: To assess the long-term safety and tolerability of esketamine nasal spray in combination with an SSRI/SNRI in participants who have completed 32 weeks of esketamine nasal spray treatment in Study 54135419TRD3013.

Estimand Scientific Question of Interest: What is the safety and tolerability of esketamine nasal spray in combination with an SSRI/SNRI in participants who have completed 32 weeks of esketamine nasal spray treatment in Study 54135419TRD3013, based on the development of treatment-emergent adverse events (AEs)?

The estimand is defined by the following 5 components:

Study Intervention: esketamine nasal spray in combination with an SSRI/SNRI

Population: participants who have completed 32 weeks of esketamine nasal spray treatment in Study 54135419TRD3013 and received at least one dose of esketamine in Study 54135419TRD4010

Variable: development of treatment-emergent AE: from the initial administration of study intervention in Study 54135419TRD3013 through the day of last dose in Study 54135419TRD4010 plus 30 days

Summary Measure: number and incidence of subjects who develop an treatment-emergent AE per person-time at risk

Intercurrent events and their corresponding strategies:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
Discontinuation of (any component of) study intervention for any reason	*While on treatment:* All AEs occurring through the day of last dose plus 30 days are included in analysis
Withdrawal from the study	*While on treatment:* Same as above

5.3.2.1. Analysis Methods

5.3.2.1.1. Primary Analysis

The verbatim terms used in the case report form by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention in Study 54315419TRD3013 through completion the participant's 2-week safety follow-up visit in Study 54135419TRD4010 is considered to be treatment emergent. Serious AEs reported within 30 days after the last dose of study intervention in Study 54135419TRD4010 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 AEs will be included in the analysis. For each AE, the number, proportion and incidence rate of participants who experience at least 1 occurrence of the given event will be summarized. The incidence rate is defined as the numbers of participants who experience at least 1 occurrence of the AE divided by the time at risk. Time at risk is defined as time from initial administration of study intervention in Study 54135419TRD3013 until first occurrence of AE or until last dose of study intervention plus 30 days (if participant did not experience AE). To calculate time at risk if the start date of an AE is missing completely or partially, following imputation rule will be applied:

If the onset date of an adverse event is missing day only, it will be set to:

i) First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of initial dosing date of Study 54135419TRD3013

ii) The day of initial dosing in Study 54135419TRD3013, if the month/year of the onset of AE is the same as month/year of the initial dose date and month/year of the AE resolution date is different

iii) The day of initial dosing in Study 54135419TRD3013 or day of AE resolution date, whichever is earliest, if month/year of the onset of AE and month/year of the initial dosing date of Study 54135419TRD3013 and month/year of the AE resolution date are the same.

If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:

i) January 1 of the year of onset, as long as this date is after the initial dosing date of Study 54135419TRD3013.

ii) one day after initial dosing date in Study 54135419TRD3013, if this date is the same year that the AE occurred.

A completely missing onset date of an adverse event will be set to the initial dosing date in Study 54135419TRD3013.

If the end date of an AE that is not recorded as ongoing is missing completely or partially, following imputation rule will be applied:

- For AEs with outcome Fatal, the AE end date is the death date
- The missing day of resolution of an adverse event will be set to the last day of the month of resolution.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earlier of the date of withdrawal, study completion, or December 31 of the year.
- A completely missing resolution date of an adverse event that is not recorded as ongoing will be set to the date of study completion/discontinuation.

For a total number of participants with treatment-emergent AEs, SAEs,… (not on SOC, PT level), the 95% confidence interval of the proportion and incidence rate will be calculated. For proportion, the 95% Clopper-Pearson confidence interval will be calculated. The 95% confidence interval of the incidence rate will be based on a Poisson model with development of treatment-emergent AE as dependent variable, an intercept and log (time at risk) as offset.

Summary tables will be provided for treatment-emergent AEs:

- AEs
- AEs (SOC, PT level only for most common TEAE) stratified by AE duration
- End date same as start date
- End date later than start date (ongoing AEs to be classified in this group)
- Serious AEs (SAEs)
- AEs leading to discontinuation of each study agent within the study intervention
- AEs by severity
- AEs by relationship to each study agent within the study intervention
- AEs leading to dose interruption/dose modification of each study agent within the 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.
- AEs of special interest (Appendix 7)

Incidence of treatment-emergent AEs 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 7 for a list of AEs in each category.

A listing of participants who died will be provided.

Duration of TEAE

Additionally a bar chart will be created to present the duration of AEs (Treatment-emergent AEs in more than 5% of patients).

Duration of AEs will be calculated as:

- If AE start date = AE end date: AE end time – AE start time
- If AE start date < AE end date: AE end date – AE start date +1
- Note: for AE with outcome FATAL: AE end date= death date

AEs are categorized in following categories

- Duration: <= 1hour
- Duration: > 1 hour to <= 2 hours
- Duration: > 2 hours to <= 3 hours
- Duration: > 3 hours to <= 8 hours
- Duration: > 8 hours but AE start date=AE end date
- Unknown: Missing duration (ie. missing start or end time) and AE start date=AE end date
- Duration: 2 days to <= 7 days
- Duration: 8 days to <=28 days
- Duration: >28 days or AE ongoing

Bar chart that shows the percentage of AEs in each category is created.

Clinically significant weight change

- Calculate the number and % of patients with an increase of at least 7% in body weight at any point in time compared to baseline. Only include visits until last dose + 14 days.
- Calculate the number and % of patients with a decrease of at least 7% in body weight at any point in time compared to baseline. Only include visits until last dose + 14 days.
- Above proportions are calculated on all patients in the safety analysis set who have baseline and at least one post-baseline body weight measurement.
- If body weight missing, assume no 7% increase/decrease from baseline.

Medication

- Calculate the number and % of patients who received any concomitant therapy for TEAE. Denominator is patients in safety analysis set with at least one TEAE.
- Calculate the number and % of patients who received any concomitant therapy for TEAE, by preferred term. Denominator is patients in safety analysis set who developed the specific preferred term as TEAE.

- Analyses are based on data on AE page (AECONTRT). If AECONTRT is missing, assume no concomitant therapy received.

Days with AE

- For each patient, calculate the number of days on which the patient had any TEAE, including only days from date of first dose of study intervention until date of last dose of study intervention inclusive. If at a certain day the patient had multiple TEAEs, this should be counted as one day. Report summary statistics (mean, SD, median, range).
- Divide the number calculated above by study intervention duration (date of last dose of study intervention – date of first dose of study intervention +1). Report summary statistics (mean, SD, median, range).
- For AEs that are ongoing (AEENRF=AFTER): AE end date will be set as date of study completion/discontinuation

TEAEs that led to dose reduction

- Calculate percentage of TEAEs that led to dose reduction: denominator is all TEAEs. Numerator is all TEAEs with action 'Dose Reduced' (AEACNS1/AEACNS2).
- Calculate percentage of TEAEs that led to dose reduction, by PT: denominator is all TEAEs of specific PT. Numerator is all TEAEs of specific PT with action 'Dose Reduced' (AEACNS1/AEACNS2).

TEAEs on dosing days

- Calculate percentage of TEAEs that occurred on dosing days, in total and on PT level
- Of TEAEs that occurred on dosing days, calculate the percentage with same day resolution, in total and on PT level.

5.3.2.1.2. Sensitivity Analysis

Not applicable

5.3.2.1.3. Supplementary Analysis

Several supplementary analyses will be performed where a selection of AEs will be included

- Only including AEs starting at or after the initial administration of study intervention in Study 54135419TRD3013 and before the day of first dose in Study 54135419TRD4010
- Only including AEs starting at or after the initial administration of study intervention in Study 54135419TRD4010 through the day of last dose in Study 54135419TRD4010 plus 30 days. Following outputs will be repeated:
    - Overall summary of TEAE
    - TEAE by SOC and PT
    - TEAE by maximum severity
    - TEAE by maximum relationship to esketamine

- Treatment-emergent SAE
- TEAE of special interest
- TEAE leading to esketamine dose interruption or change
- TEAE stratified by AE duration (end date same as start date versus end date later than start date)
- Summary of days with TEAE
- Proportion of TEAEs occurring on dosing days
- Proportion of TEAEs which occur on dosing days with same day resolution

- Only including AEs starting at or after the initial administration of study intervention in Study 54135419TRD3013 through the day on which there is a switch of SSRI/SNRI or the day of last dose in Study 54135419TRD4010 plus 30 days, whichever comes first
- Only including AEs starting at or after the initial administration of study intervention in Study 54135419TRD4010 through the day on which there is a switch of SSRI/SNRI or the day of last dose in Study 54135419TRD4010 plus 30 days, whichever comes first

5.3.3. Estimand for C-SSRS

The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed to assess severity and track suicidal events through any intervention (Posner 2007). It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS has been used frequently in clinical studies, and is a validated, standard measure for suicidal ideation assessment. Using the C-SSRS, the outcomes will be categorized using the scoring for the 11 categories:

Suicidal Ideation (1-5)	
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent
Suicidal Behavior (6-10)	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt
9	Actual attempt
10	Suicide
Non-suicidal self-injurious behavior (11)	
11	Non-suicidal self-injurious behavior

If no events qualify for a score of 1 to 10, a score of 0 will be assigned (0="no suicidal ideation or behavior that can be assessed on the basis of C-SSRS"). A participant with a score of 11 will be considered as not having suicidal ideation or behavior.

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.

Primary Trial Objective: To assess the long-term safety and tolerability of esketamine nasal spray in combination with an SSRI/SNRI in participants who have completed 32 weeks of esketamine nasal spray treatment in Study 54135419TRD3013.

Estimand Scientific Question of Interest: What is the safety and tolerability of esketamine nasal spray in combination with an SSRI/SNRI in participants who have completed 32 weeks of esketamine nasal spray treatment in Study 54135419TRD3013, based on the C-SSRS?

The estimand is defined by the following 5 components:

Study Intervention: esketamine nasal spray in combination with an SSRI/SNRI

Population: participants who have completed 32 weeks of esketamine nasal spray treatment in Study 54135419TRD3013

Variable: Number of participants who Shift from the baseline visit in Study 54135419TRD3013 to the maximum postbaseline C-SSRS score

Summary Measure: frequency distribution

Intercurrent events and their corresponding strategies:

Intercurrent Events	**Name of Strategy for Addressing Intercurrent Events and Its Description**
Discontinuation of (any component of) study intervention for any reason	*While on treatment:* Only C-SSRS values up to the date of the last dose will be used.
Withdrawal from the study	*While on treatment:* Same as above

5.3.3.1. Analysis Methods

5.3.3.1.1. Primary Analysis

Shift from the baseline visit in Study 54135419TRD3013 to the maximum postbaseline score pertaining to suicidal ideation or suicidal behavior (i.e., scores 1 to 10) will be summarized.

The maximum score (of scores 1 to 10) assigned to each participant will be grouped into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Participants with only a score of 11, ie. no scores between 1 to 10, will be classified a No suicidal ideation or behavior. Shifts from the baseline visit in Study 54135419TRD3013 to the maximum postbaseline category will be summarized.

A frequency distribution of the scores for the 11 categories and the 3 composite endpoints will be provided at each time point.

For the suicidal ideation score the shift from baseline visit in the 54135419TRD3013 study to the maximum during treatment will be summarized.

5.3.3.1.2. Sensitivity Analysis

Not applicable

5.3.3.1.3. Supplementary Analysis

Not applicable

5.4. Secondary Endpoint(s) Analysis

5.4.1. Relapse

5.4.1.1. Definition

A participant is defined as a remitter at a given time point if the MADRS total score is ≤10 at that time point.

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 31 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 secondary endpoint is no relapse until the end of the prospective observation period at Week 104 visit (or end-of-study) visit, and no discontinuation of (any component of) study intervention within group of subjects who are in remission at Week 8 visit of Study 54135419TRD3013.

To be aligned with ESCAPE-TRD study, 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.

5.4.1.2. Analysis Methods

The efficacy analysis of data will be based on the Safety/Efficacy analysis set.

The proportion of subjects with the secondary endpoint (as defined above) will be estimated together with 95% Clopper-Pearson confidence interval. The incidence rate of subjects with the secondary endpoint (as defined above) will be estimated together with 95% confidence interval. The incidence rate is defined as the number of subjects who achieve the secondary endpoint divided by the time at risk. Time at risk is defined as time from Week 8 visit in Study 54135419TRD3013 until last visit date. The 95% confidence interval of the incidence rate will be calculated based on a Poisson model with achievement of secondary enpoint as dependent variable, an intercept and log (time at risk) as offset.

The remission time point is the first time point at which the participant is in remission. This analysis will only include participants for whom the remission time point is before or at Week 32 of Study 54135419TRD3013. 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.

A frequency table of the number of relapses for subjects in remission at Week 8 of Study 54135419TRD3013 will be made. A frequency table of the number of relapses for subjects in remission at any time point during Study 54135419TRD3013 will be made. A frequency table of the number of relapses for subjects who were not in remission during Study 54135419TRD3013 but who are in remission at any time point during Study 54135419TRD4010 will be made

The relapse narratives of relapses during Study 54135419TRD4010 will be listed.

5.4.2. Montgomery-Asberg Depression Rating Scale (MADRS)

5.4.2.1. Definition

The MADRS is a clinician-administered scale designed to measure depression severity and detects changes due to antidepressant intervention. (Montgomery 1979) The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms). Higher scores represent a more severe condition. The MADRS evaluates reported sadness, apparent sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability. The typical recall period for the MADRS is 7 days.

The MADRS total score is the sum of scores from individual question items at a given time point, and ranges from 0 to 60. Higher scores represent 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.

Negative changes in MADRS total score indicate improvement.

5.4.2.2. Analysis

Descriptive statistics of the actual values and the change from Study 54135419TRD3013 baseline to each postbaseline time point will be presented for MADRS total score and the individual depressive symptoms. Summaries of observed data will be presented. Mean score (+/- SE) and mean changes from baseline (+/- SE) of MADRS total score will be presented graphically over time.

5.4.3. Response Based on MADRS Total Score

5.4.3.1. Definition

A participant is defined as a responder at a given time point if the percent improvement from Study 54135419TRD3013 baseline in MADRS is ≥50% at that time point (i.e., percent change ≤-50%) or if the MADRS total score is ≤10. Participants who do not meet such criterion will be considered as non-responders.

5.4.3.2. Analysis

The number and percentage of participants who achieve a response will be summarized at each time point for observed case data.

5.4.4. Remission Based on MADRS Total Score

5.4.4.1. Definition

See Section 5.4.1.1.

5.4.4.2. Analysis

The number and percentage of participants who achieve remission will be summarized at each time point for observed case data.

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

5.4.5.1. Definition

The CGI-S provides an overall clinician-determined summary measure of the severity of the participant's illness that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function. (Guy 1991) The CGI-S evaluates the severity of psychopathology on a scale of 1 to 7. Considering total clinical experience with the depression population, a participant is assessed on severity of illness at the time of rating according to: [0=not assessed; 1=normal (not at all ill); 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients].

A score of 0 indicates that the participant was not assessed, and will be treated as missing. The score from 1 to 7 will be summarized as recorded.

Negative changes in CGI-S score indicate improvement.

5.4.5.2. Analysis

Descriptive statistics of the actual values and the change from Study 54135419TRD3013 baseline will be presented for observed case data.

Mean score (+/- SE) and mean changes from baseline (+/- SE) will be presented graphically over time.

A frequency distribution over time of the CGI-S scores at each scheduled visit will be provided for observed case data.

5.4.6. Patient Health Questionnaire - 9 Item (PHQ-9)

5.4.6.1. Definition

The 9-item Patient Health Questionnaire - 9 Item (PHQ-9) scale scores each of the 9 symptom domains of the DSM-5 MDD criteria and it has been used both as a screening tool and a measure of response to intervention for depression. 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. The recall period is 2 weeks.

Negative changes in PHQ-9 total score indicate improvement.

5.4.6.2. Analysis

Descriptive statistics of the actual values and the change from Study 54135419TRD3013 baseline to each postbaseline time point will be presented for PHQ-9 total score for observed case data. Mean total score (+/- SE) and mean changes from baseline (+/- SE) will be presented graphically over time.

Frequency distributions of the responses to the question "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" will be provided at each assessment time point for observed case data.

5.4.7. Response Based on PHQ-9 Total Score

5.4.7.1. Definition

A participant is defined as a responder at a given time point if the percent improvement from Study 54135419TRD3013 baseline in PHQ-9 total score is ≥50% at that time point. Participants who do not meet such criterion will be considered as non-responders.

Negative percent changes in PHQ-9 total score indicate improvement (eg, percent change < -50% indicates improvement >50%).

5.4.7.2. Analysis

The number and percentage of participants who achieve response will be summarized at each time point for observed case data.

5.4.8. Remission Based on PHQ-9 Total Score

5.4.8.1. Definition

A participant is defined as a remitter at a given time point if the PHQ-9 total score is ≤9 at that time point. Participants who do not meet such criterion will be considered as non-remitters. As a sensivity analysis, remission will be defined as a PHQ-9 total score ≤4.

5.4.8.2. Analysis

The number and percentage of participants who achieve a remission of depressive symptoms will be summarized at each time point for observed case data.

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

5.4.9.1. Definition

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome, primarily designed for self-completion by respondents. It is a descriptive system comprised of 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 indicating no problem, Level 2 indicating slight problems, Level 3 indicating moderate problems, Level 4 indicating

severe problems, and Level 5 indicating extreme problems). (EuroQol Group 2014, EuroQol Group 2013)

Participants select an answer for each of the 5 dimensions considering the response that best matches their health "today". Individual scores from the 5 dimensions will be used to obtain a weighted health status index as shown below: (i) Scores from each dimension will be combined to obtain a 5L profile score: eg, a score of 1 for each dimension will give a 5L profile score 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*".

A sum score, with a possible range of 0 to 100, is derived as follows: (sum of the scores from the 5 dimensions minus 5) * 5. Negative changes in the sum score indicate improvement.

5.4.9.2. Analysis

Descriptive statistics of the actual values and the change from Study 54135419TRD3013 baseline to each postbaseline time point will be presented for weighted EQ-5D health status index, the EQ-VAS, and the sum score for observed case data. Mean values and mean changes from baseline (+/- SE) will be presented graphically over time.

Individual dimension responses will also be summarized at each visit with frequency counts and percentage of participants for observed case data.

5.5. Exploratory Endpoint(s) Analysis

In cases where the oral AD is switched to another compound from the SNRI/SSRI classes during Study 54135419TRD4010, the impact of switching will be explored. The reasons for the switches will be summarized, the impact on existing AEs will be described (outcome of AEs ongoing at the time of switching will be tabulated), and new AEs starting after the switches will be tabulated. Also, the impact on the efficacy parameters MADRS and CGI-S will be explored by summarizing the observed values at the visit when the switch was made and changes from that visit at subsequent visits. Furthermore, a listing will be created for the participants who switch to another compound from the SNRI/SSRI classes during Study 54135419TRD4010.

5.6. Other Safety Analyses

All safety analyses will be based on the Safety analysis set using data from Study 54135419TRD3013 and Study 54135419TRD4010, unless otherwise specified.

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

5.6.1. Extent of Exposure

Total exposure during both Study 54135419TRD3013 and Study 54135419TRD4010 is described, unless specified otherwise.

The number and percentage of participants who receive each study agent within the 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.

Modal dose for a subject is defined as the most frequently taken dose by a subject. Mean dose of a subject is calculated as the sum of doses divided by the total number of days. The final dose is the last non-zero dose received. The calculation of mean, modal and final dose will exclude days off study drug.

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

For esketamine NS, the number (%) of participants with a dose adjustment/dose frequency adjustment/dose not administered during Study 54135419TRD4010 will be summarized. Reasons for doses not administered will also be summarized. For oral AD, the number (%) of participants with a dose adjustment during Study 54135419TRD4010 will be summarized. Reasons for dose adjustments will also be summarized.

The number (%) of participants with a swith of oral AD during Study 54135419TRD4010 will be summarized.

5.6.1.1. 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.

Exposure to study intervention is described in section 5.6.1.

5.6.2. Adverse Events

See section 5.3.2

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinically significantly abnormal laboratory results are recorded as an AE and will be reported in Section 5.3.2.

5.6.3.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including weight, respiratory rate, pulse, and blood pressure (systolic and diastolic) will be summarized at each assessment time point. If the time point (pre-dose/post-dose) is missing, this will be derived from the vital sign assessment time and the esketamine administration time. Change from baseline in Study 54135419TRD3013 will be summarized. Descriptive statistics (mean, SD, median, minimum and maximum) will be presented.

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 below) will be applied to baseline and postbaseline post-dose values. For baseline values, increase or decrease criteria are not applied.

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

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

- Treatment-emergent 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.

Proportion and incidence rate of treatment-emergent clinically important vital signs during intervention, as defined in Table 02, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign.

Table 02: 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;

The proportion and incidence rate of subjects who experienced treatment-emergent acute hypertension (systolic BP ≥ 180 or diastolic BP ≥ 110) at any time during Study 54135419TRD3013 or Study 54135419TRD4010 will be summarized.

The incidence rate is defined as the number of subjects who achieve the event divided by the time at risk. Time at risk is defined as time from initial administration of study intervention in Study 54135419TRD3013 until last visit date.

5.6.3.3. Electrocardiogram

Not applicable

5.6.3.4. 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.

5.6.3.5. Pregnancy testing

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

5.6.3.6. Other Safety Parameters

5.6.3.6.1. Columbia Suicide Severity Rating Scale (C-SSRS)

See section 5.3.3

5.7. Other Analyses

5.7.1. Pharmacokinetics

Not applicable

5.7.2. Immunogenicity

Not applicable

5.7.3. Pharmacodynamics

Not applicable

5.7.4. Pharmacokinetic/Pharmacodynamic Relationships

Not applicable

5.7.5. Biomarkers

Not applicable

5.7.6. Health Economics

Not Applicable

5.7.6.1. Healthcare Resource Use Questionnaire (HRUQ)

5.7.7. Other Variables and/or Parameters

5.7.7.1. Definition

5.7.7.2. Analysis Method

5.7.8. Definition of Subgroups

The primary and secondary endpoints will be analyzed as described in the respective sections for the following subgroups.

Subgroup	Variant	Definition
Sex		Male Female
Age Group		Adult [18-64] Elderly [>=65]
Number of previous treatment failures		2 >=3
Class of continued oral AD at baseline		SNRI SSRI
Race		White Other
Region		Africa Asia Pacific Europe South America

5.8. Interim Analyses

The protocol states:

An interim analysis may be performed after approximately 50 participants have been enrolled in the study, when data have been accrued over a period of 9 to 12 months.

Other interim analyses may be planned based on specific questions from the medical field or from health authorities in certain countries.

However it is decided to not perform an interim analysis.

5.8.1. Independent Data Monitoring Committee (IDMC) or Other Review Board

Not applicable

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: List of Abbreviations

AD	Antidepressant
AE	adverse event
ATC	anatomic and therapeutic class
CGI-S	Clinical Global Impression – Severity
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
EQ-5D-5L	European Quality of Life (EuroQol) Group, 5 Dimension, 5-Level
IDMC	Independent Data Monitoring Committee
IQ	interquartile
MADRS	Montgomery-Asberg Depression Rating Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model for Repeated Measures
MNAR	Missing not at random
PHQ-9	Patient Health Questionnaire - 9 Item
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SNRI	serotonin and norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor

6.2. Appendix 2: Changes to Protocol-Planned Analyses

The protocol states:

An interim analysis may be performed after approximately 50 participants have been enrolled in the study, when data have been accrued over a period of 9 to 12 months.

Other interim analyses may be planned based on specific questions from the medical field or from health authorities in certain countries.

However it is decided to not perform an interim analysis.

6.3. Appendix 3: Demographics and Baseline Characteristics

Table 03 presents a list of the demographic variables at enrollment in Study 54135419TRD3013 that will be summarized for the Safety/Efficacy analysis set.

Table 03: Demographic Variables

Continuous Variables	**Summary Type**
Age ([years])	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and interquartile (IQ) range).
Weight (kg)	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
Age (18-64 years, and >=65 years)	
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)	

6.4. Appendix 4: Protocol Deviations

Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category for the Safety/efficacy analysis set. A listing of all major protocol deviations will be presented.

6.5. Appendix 5: Prior and Concomitant Medications

Prior medications and concomitant medications will be coded using the World Health Organization Drug Dictionary. Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention in Study 54135419TRD3013. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention in Study 54135419TRD3013, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC term. 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.

Prior medications will be summarized by ATC term.

6.6. Appendix 6: Medical History

The following variables will be summarized for subjects who experienced any past and/ or concomitant diseases at screening in Study 54135419TRD3013:

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: Adverse Events of Special Interest

Adverse events of special interest are defined as follows:

AE Special Interest Category	Preferred Term
Sedation	sedation
Sedation	somnolence
Sedation	altered state of consciousness
Sedation	depressed level of consciousness
Sedation	hypersomnia
Sedation	stupor

AE Special Interest Category	Preferred Term
Dissociation	depersonalisation/derealisation disorder
Dissociation	derealisation
Dissociation	dissociative disorder
Dissociation	flashback
Dissociation	hallucination
Dissociation	hallucination, auditory
Dissociation	hallucination, visual
Dissociation	illusion
Dissociation	somatic hallucination
Dissociation	hyperacusis
Dissociation	tinnitus
Dissociation	diplopia
Dissociation	vision blurred
Dissociation	ocular discomfort
Dissociation	photophobia
Dissociation	visual impairment
Dissociation	dysaesthesia
Dissociation	oral dysaesthesia
Dissociation	paraesthesia
Dissociation	paraesthesia oral
Dissociation	pharyngeal paraesthesia
Dissociation	time perception altered
Dissociation	daydreaming
Dissociation	delusional perception
Dissociation	feeling hot
Dissociation	feeling cold
Dissociation	feeling of body temperature change

AE Special Interest Category	Preferred Term
Suicidality	completed suicide
Suicidality	depression suicidal
Suicidality	intentional overdose
Suicidality	intentional self-injury
Suicidality	multiple drug overdose intentional
Suicidality	poisoning deliberate
Suicidality	self-injurious behavior
Suicidality	self-injurious ideation
Suicidality	suicidal behavior
Suicidality	suicidal ideation
Suicidality	suicide attempt
Suicidality	toxicity to various agents

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

AE Special Interest Category	Preferred Term
Cystitis	adenoviral hemorrhagic cystitis
Cystitis	allergic cystitis
Cystitis	bladder candidiasis
Cystitis	bladder diverticulitis
Cystitis	cystitis bacterial
Cystitis	cystitis erosive
Cystitis	cystitis escherichia
Cystitis	cystitis glandularis
Cystitis	cystitis gonococcal
Cystitis	cystitis helminthic
Cystitis	cystitis hemorrhagic
Cystitis	cystitis interstitial
Cystitis	cystitis klebsiella
Cystitis	cystitis noninfective
Cystitis	cystitis pseudomonal
Cystitis	cystitis radiation
Cystitis	cystitis ulcerative
Cystitis	cystitis viral
Cystitis	emphysematous cystitis
Cystitis	eosinophilic cystitis
Cystitis	fungal cystitis
Cystitis	lupus cystitis
Cystitis	malacoplakia vesicae
Cystitis	schistosomiasis bladder
Cystitis	trigonitis
Cystitis	tuberculosis bladder
Cystitis	urinary bladder abscess
Cystitis	viral hemorrhagic cystitis

AE Special Interest Category	Preferred Term
Hepatic impairment	acquired complement deficiency disease
Hepatic impairment	bilirubin excretion disorder
Hepatic impairment	crigler-najjar syndrome
Hepatic impairment	HELLP (hemolysis, elevated liver enzymes, and a low platelet count) syndrome
Hepatic impairment	hepatic function abnormal
Hepatic impairment	hyperammonemic crisis
Hepatic impairment	hyperammonemia
Hepatic impairment	hypertransaminasemia
Hepatic impairment	hypoalbuminemia
Hepatic impairment	hypoproteinemia

7. REFERENCES

EuroQol Group. About EQ-5D. http://www.euroqol.org/about-eq-5d.html (Accessed 18 Jun 2014).

EuroQol Group. EQ-5D-5L User Guide: basic information on how to use the EQ-5D-5L instrument. Version 2.0; Oct 2013. http://www.euroqol.org/fileadmin/user_upload/Documenten/PDF/Folders_Flyers/UserGuide_EQ-5D-5L_v2.0_October_2013.pdf (Accessed 6 Aug 2014).

Guy W. CGI: Clinical Global Impressions. In: ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Department of Health and Human Services; printed 1976 (reprinted 1991):217-222.

Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035-1043.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). [2009] Guidance for industry drug induced liver injury: premarketing clinical evaluation. Available: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf.