**Janssen Research & Development**

# Statistical Analysis Plan
# Amendment 1

## A Randomized, Double-blind, Multicenter, Placebo-controlled Study of Adjunctive Aticaprant Plus an Antidepressant for Relapse Prevention in Major Depressive Disorder (MDD) With Moderate-to-severe Anhedonia

**Protocol 67953964MDD3005; Phase 3**

**JNJ-67953964 (aticaprant)**

Status: Approved
Date: 17 June 2025
Prepared by: Janssen Research & Development,
LLC Document No.: EDMS-RIM-1430387; 2.0

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

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# VERSION HISTORY

**Table – SAP Version History Summary**

| SAP Version | Approval Date | Change | Rationale |
|---|---|---|---|
| 1.0 | 10 Dec 2024 | Not Applicable | Initial release |
| 2.0 | 17 June 2025 | Remove the following analyses:<br>- Hypothesis testing and estimand languages for primary and key secondary endpoints<br>  - Interim analysis<br>  - Multiplicity adjustment<br>  - Analyses for efficacy endpoints<br>  - Subgroup analyses and psychiatry disease characteristic which are not needed for the abbreviated CSR<br>PK and biomarker analyses | This study is prematurely terminated due to sponsor's decision. The final analyses will be descriptive in nature for all safety data. Other analyses which are not needed for the abbreviated CSR are removed. |

# 1. INTRODUCTION

Johnson & Johnson has taken a decision to discontinue development of aticaprant (JNJ- 67953964) as an adjunctive treatment in Major Depressive Disorders (aMDD) due to insufficient efficacy in recently completed phase 3 interventional trials. Accordingly, the ongoing 67953964MDD3005 study was prematurely terminated. This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all necessary safety analyses for study 67953964MDD3005. Analyses for efficacy and other exploratory endpoints stated in the protocol will not be performed unless otherwise specified.

Analyses for the open-label (OL) phase are described. Analyses for double-blind (DB) phase will be presented in listings only.

## 1.1. Objectives and Endpoints

**OBJECTIVES AND ENDPOINTS**

Due to study termination, analyses pertaining to the following objectives stated in the protocol will not be performed: primary, secondary and exploratory objectives in the double-blind treatment phase, efficacy objectives in the open-label phase, additional exploratory objectives related to clinical pharmacology and biomarker signatures. The table below provides a list of objectives and endpoints that will be evaluated.

| Objectives | Endpoints |
|---|---|
| **Safety** | |
| Safety will be assessed in all participants. | |
| To assess the safety and tolerability of aticaprant 10 mg once daily (all treatment phases) as adjunctive therapy to an antidepressant in participants with MDD ANH+ in the OL phase | • AEs including AESIs<br>• Vital signs including weight, BMI<br>• Suicidality assessment using the C-SSRS<br>• Laboratory values and ECGs |

## 1.2. Study Design

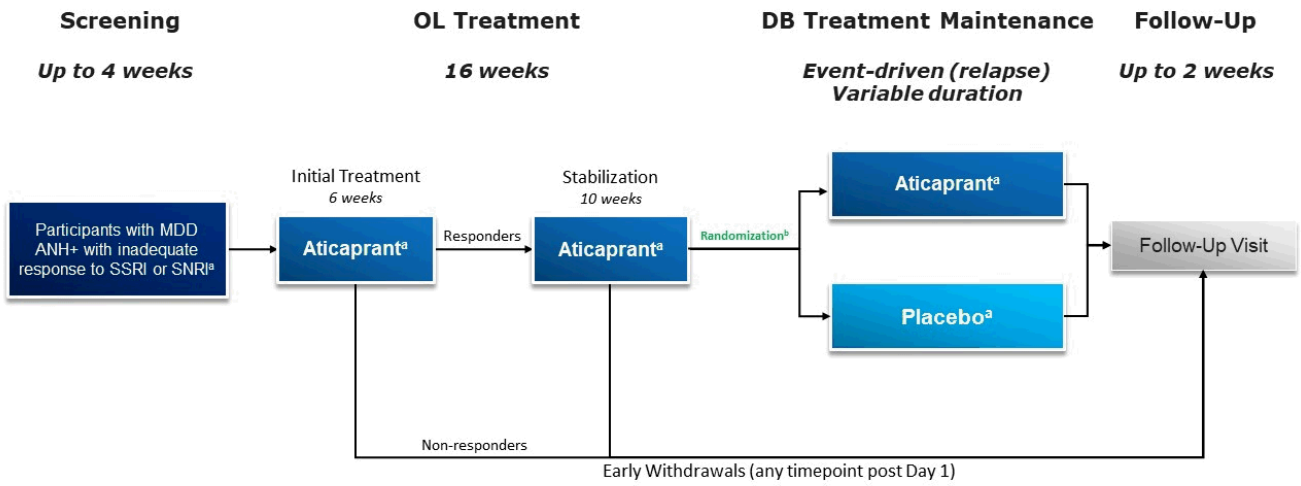
This is a randomized, DB, placebo-controlled, parallel-group, multicenter study to assess the efficacy of aticaprant 10 mg as adjunctive therapy to an SSRI/SNRI antidepressant in delaying relapse of depressive symptoms in adult participants with MDD ANH+ who achieve a stable response after 16 weeks of OL treatment (initial treatment and stabilization) with adjunctive aticaprant.

In addition, safety, PK, PD, and biomarkers will be evaluated.

The study will consist of the following phases (Figure 1):

- Screening phase (to evaluate eligibility): up to 30 days prior to first dose administration
- OL initial treatment phase: 6 weeks
- OL treatment stabilization phase: 10 weeks
- DB treatment maintenance phase: variable duration
- Follow-up phase: up to 2 weeks

**Figure 1: Schematic Overview of the Study**




[a] All participants will continue to take their current SSRI or SNRI antidepressant (one only) throughout the study.
[b] Stable responders will be randomized to aticaprant or placebo. Participants not meeting the blinded definition for stable response will have sham randomization and continue receiving aticaprant.

**Abbreviations:** ANH+ = moderate-to-severe anhedonia; DB= double-blind; MDD = Major Depressive Disorder; OL = open-label; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor.

The proposed study population includes participants from the general MDD population (adults aged 18-64 years, inclusive) with an inadequate response to their current ongoing standard-of-care antidepressant (SSRI/SNRI) who are moderately to severely depressed and ANH+.

The SIQA will also assess the validity of the participants' current MDE, symptom severity, and antidepressant treatment response for inclusion in the study. The SIQA is a tool to facilitate participant selection for MDD clinical studies, with a goal to ensure enrollment of participants who have symptoms that reflect the current state of illness and that these symptoms can be reliably measured with appropriate measurement tools, as well as to minimize the placebo response.

All participants will receive aticaprant 10 mg during the OL treatment phases. Criteria defining stable response at the end of the OL treatment stabilization phase are blinded to the sites and are provided in an addendum to the study protocol. Participants who are stable responders after a total of 16 weeks of treatment in the OL treatment phases, will be randomly assigned to receive adjunctive aticaprant 10 mg or adjunctive placebo in the DB treatment maintenance phase. Additionally, since the criterion for stable response is blinded to the sites, participants who do not meet criteria for stable response at the end of the OL treatment stabilization phase will also proceed into the DB treatment maintenance phase using a sham randomization and will continue to receive aticaprant 10 mg.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. A 1:1 (adjunctive placebo: adjunctive aticaprant 10 mg) randomization ratio will be used. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

## 2. STATISTICAL HYPOTHESES

As the study was prematurely terminated, efficacy analyses pertaining to the hypothesis of the study will not be conducted.

## 3. SAMPLE SIZE DETERMINATION

The maximum number of events required for the study is approximately 127, which provides 90% power to detect a hazard ratio of 0.562 at the 1-sided significance level of 0.025 (equivalent to 2-sided 0.05), to detect superiority of aticaprant compared with placebo (both as an adjunctive treatment) in delaying relapse of depressive symptoms in adult participants with MDD ANH+ who are stable responders. Time to the first relapse is assumed to follow an exponential distribution with 6-month relapse rates of 37% for adjunctive placebo and 22.9% for adjunctive aticaprant. A hazard ratio of 0.562 is considered clinically meaningful based on discussions with external clinical experts. The placebo relapse rate is based on literature review of similarly designed studies in MDD population (Goodwin 2009; Gorwood 2007; Liebowitz 2010; Rapaport 2004).

A total of approximately 330 participants with stable response will need to be randomized (in a 1:1 ratio to either continue with adjunctive aticaprant 10 mg or receive adjunctive placebo after discontinuation of adjunctive aticaprant) to obtain approximately 127 relapse events based on the following:

- Assumption of an accrual period of 24 months and a DB treatment maintenance phase duration of 26 months (this is the assumed duration of the DB treatment maintenance phase of the study as a whole, not for each participant). The assumed durations are only for the purpose of sample size estimation and not restrictions on the actual study duration.
- Participants are followed until relapse, discontinuation, or end of study.
- 25% drop-out rate in each group over 6 months.

It is anticipated that out of the 330 participants randomized in the DB treatment maintenance phase, approximately 182 participants will be evaluable for the assessment of SF. If the hypothesis for the primary endpoint is rejected, the study is powered at 80% to detect an effect size of 0.44 for the change in CSFQ

-14 total score at Week 4 in the DB treatment maintenance phase.

The actual number of participants randomized will depend on the length of time it takes to obtain the necessary number of relapse events. Blinded surveillance of the total number of relapse events in the DB treatment maintenance phase will be performed during the study to assess the appropriateness of the assumptions regarding accrual and drop-out rates. Assuming a stable response rate of 50%, approximately 660 participants are expected to be enrolled in the OL initial treatment phase of the study in order to obtain 330 stable responders for the DB treatment maintenance phase. The number of participants enrolled and the number of participants who discontinue before entering the DB treatment maintenance phase will be closely monitored. Additionally, if there is an insufficient number of participants who are evaluable for assessment of SF, enrollment may continue until there are 182 participants evaluable for the key secondary endpoint or up to a maximum of 127 relapses have been reported for the primary endpoint.

However, the study was terminated before the required number of 330 participants have been randomized to the DB phase.

## 4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

For purposes of analysis, the following analysis sets are defined.

| Population | Abbreviation | Description |
|---|---|---|
| Enrolled | Enrolled | All participants who sign the ICF. |
| Safety Analysis Set – Open label treatment phase | SAF (OL) | All participants who take at least 1 dose of study intervention in the OL initial treatment phase. |
| Safety Analysis Set – Open label treatment stabilization phase | SAF (ST) | All participants who take at least 1 dose of study intervention in the OL treatment stabilization phase. |
| Randomized | Randomized | All participants who are randomized to Double-blind phase |
| Follow-up Analysis Set | | All participants who enter the follow-up phase. |

The safety analyses will be based on the safety analysis sets.

# 5. STATISTICAL ANALYSES

## 5.1. General Considerations

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

### 5.1.1. Analysis Phases

Screening Phase

The analysis reference start date of the screening phase is the date when participant signed informed consent. The analysis reference end date of the screening phase is the day prior to the first dose of study intervention in the OL initial treatment phase.

OL Initial Treatment Phase

The analysis reference start date of the initial treatment phase is the day of the first dose of study intervention in the OL initial treatment phase (OL initial treatment phase start date). For the participants who continue to the OL treatment stabilization phase, the analysis reference end date of the OL initial treatment phase (OL initial treatment phase end date) is the date of the first dose of study intervention in the OL treatment stabilization phase. For participants who don't enter the OL treatment stabilization phase, the analysis reference end date of the OL initial treatment phase is the maximum of the date of the last visit in the OL initial treatment phase and date of completion or early withdrawal from this phase.

OL Treatment Stabilization Phase

The analysis reference start date of the OL treatment stabilization phase is the day of the first dose of study intervention in the OL treatment stabilization phase, i.e. the medication which was administered after Visit 2.5. For the participants who continue to the DB treatment maintenance phase, the analysis reference end date of the OL treatment stabilization phase (OL treatment stabilization phase end date) is the date of the first dose of study intervention in the DB treatment maintenance phase. For participants who don't enter the DB treatment maintenance phase, the analysis reference end date of the OL

treatment stabilization phase is the maximum of the date of the last visit in the OL treatment stabilization phase and date of completion or early withdrawal from this phase.

DB Treatment Maintenance Phase

Start and end dates for the DB treatment maintenance phase are defined for participants who enter this phase, including those who are stable responders and those who don't meet the criteria for stable response. The analysis reference start date of the DB treatment maintenance phase (DB treatment maintenance phase start date) is the date of the first dose of study intervention in this DB maintenance phase. The analysis reference end date of the DB treatment maintenance phase (DB treatment maintenance phase end date) is the maximum of the date of the last visit in the DB treatment maintenance phase and date of completion or early withdrawal from this phase.

For randomized participants who do not receive any study intervention in the DB treatment maintenance phase, both analysis reference start and end dates are missing for this phase.

Follow-up (FU) Phase

Start and end dates for the FU phase are only defined for participants who continue into the FU phase. The analysis reference start date of the FU phase (FU phase start date) is the day after the reference end date for the OL initial treatment, OL treatment stabilization, or DB treatment maintenance phase. The analysis reference end date of the FU phase (FU phase end date) is the maximum of the date of the last visit in the FU phase and trial disposition.

### 5.1.2. 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. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a participant has 2 or more actual visits in a 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. 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. Listed below (Table 1) are the analysis visit windows and the target days for each visit defined in the protocol.

**Table 1: Visit Windows**

| Parameter | Analysis Phase | Scheduled day | Scheduled Visit Number | Time Interval (label on output) | Time Interval (Day)* | Target Time Point (Day)* |
|---|---|---|---|---|---|---|
| ECG, Hematology, chemistry, Urinalysis | SCR | | 1.1 | Screening | <1 | |
| | IN | 1 | 2.1 | Baseline (OL) | ≤1 | 1 |
| | | 43 | 2.5 | Day 43 (IN) | 2 to End of the OL initial treatment phase | 43 |
| | | 43 | | Endpoint (IN) | 2 to End of the OL initial treatment phase | |
| | | 113 | 3.5 | Week 10 (ST) | 2 to End of the OL stabilization treatment phase | 71 |
| | | 113 | | Endpoint (ST) | 2 to End of the OL stabilization treatment phase | |
| | | | | | | |
| Vital signs | SCR | | 1.1 | Screening | <1 | |
| | IN | 1 | 2.1 | Baseline OL) | ≤1 | 1 |
| | | 43 | 2.5 | Day 43 (IN) | 2 to End of the OL initial treatment phase | 43 |
| | | 43 | | Endpoint (IN) | 2 to End of the OL initial treatment phase | |
| | | 113 | 3.5 | Week 10 (ST) | 2 to End of the OL stabilization treatment phase | 71 |
| | | 113 | | Endpoint (ST) | 2 to End of the OL stabilization treatment phase | |
| | FU* relative to End of IN/ST | | 5.2 | Week 10 (FU) | 44 to 99 | 71 |
| | | | 5.X+2<br>X=1, 2, 3,… | Week X*8 + 10 (FU) | 44 + X*56 to 99+X*56 | 71 + X*56 |
| | | | | | | |
| C-SSRS | SCR | | 1.1 | Screening | <1 | |
| | IN | 1 | 2.1 | Baseline (OL) | ≤1 | 1 |
| | | 8 | 2.2 | Day 8 (IN) | 2 to 11 | 8 |
| | | 15 | 2.3 | Day 15 (IN) | 12 to 22 | 15 |
| | | 29 | 2.4 | Day 29 (IN) | 23 to 36 | 29 |
| | | 43 | 2.5 | Day 43 (IN) | 37 to End of the OL initial treatment phase | 43 |
| | | | | Endpoint (IN) | 2 to End of the OL initial treatment phase | |
| | | 57 | 3.1 | Week 2 (ST) | 2 to 22 | 15 |
| | | 71 | 3.2 | Week 4 (ST) | 23 to 36 | 29 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 85 | 3.3 | Week 6 (ST) | 37 to 50 | 43 |
| | | 99 | 3.4 | Week 8 (ST) | 51 to 64 | 57 |
| | | 113 | 3.5 | Week 10 (ST) | 65 to End of the OL stabilization treatment phase | 71 |
| | | 113 | | Endpoint (ST) | 2 to End of the OL stabilization treatment phase | |
| | FU* relative to End of IN/ST | | 5.1 | Week 2 (FU) | 2 to 43 for those subjects who are relapse free and transferred to FU visit;<br>2 to End of FU for others | 15 |
| | | | 5.2 | Week 10 (FU) | 44 to 99 | 71 |
| | | | 5.X+2<br>X=1, 2, 3,… | Week X*8 + 10 (FU) | 44 + X*56 to 99+X*56 | 71 + X*56 |

*Relative to the first day of the relevant phase. For the follow-up phase, time interval is relative to the first day of the follow-up phase, and Day 11 in this phase will be considered as target day if there are multiple assessments.

Relative day: (event date – analysis phase start date + 1) for an event occurring on or after the analysis phase start date; (event date – analysis phase start date) for an event prior to the analysis phase start date.

### 5.1.3. Imputation of Efficacy

Imputation of total scores will be performed for the efficacy scales as shown in Table 2 below. If the number of items with missing scores is greater than the maximum number of items that can be missing (as presented in the table), the total score will be missing.

For the remaining efficacy assessments which require adding multiple item scores, the total score will be missing if any item score is missing.

**Table 2: Imputation of Total Score for Efficacy Scales**

| Efficacy Scale | Total Number of Items | Maximum Number of Items That Can Be Missing | Formula for Total Score |
|---|---|---|---|
| MADRS | 10 | 1 | Sum of non-missing item scores * (10 / number of non-missing |

### 5.1.4. Definition of baseline

Baseline (OL) is the last assessment before the first intake of aticaprant in the OL initial treatment phase.

## 5.2. Participant Dispositions

The number of screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized for FAS (OL):

- Participants who completed, discontinued and reasons for discontinuation of study intervention in the OL initial treatment phase.
- Participants who enter the OL treatment stabilization phase
- Participants who completed, discontinued and reasons for discontinuation of study intervention in the OL treatment stabilization phase.

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention in the OL initial treatment phase
- Participants who discontinued study intervention in the OL treatment stabilization phase

## 5.3. Efficacy Parameters

### 5.3.1. Montgomery-Asberg Depression Rating Scale (MADRS)

The MADRS is a clinician-administered scale designed to measure depression severity and detects changes due to antidepressant intervention. 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, sleep, 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. The MADRS total score will be set to be missing if any item is missing. Negative changes in MADRS total score indicate improvement.

### 5.3.2. Sexual Functioning Questionnaire - Short-Form (CSFQ-14)

The CSFQ-14 was developed and validated to assess treatment-emergent sexual dysfunction in MDD patient populations. There are separate versions for males and females. The scale uses 5-point Likert response options to provide the patient an opportunity to self-evaluate his or her sexual behaviors or problems in a number of areas. For all items, higher scores reflect higher sexual functioning (Keller 2006). For 12 of the 14 items, higher sexual functioning corresponds to greater frequency or enjoyment/pleasure (eg, 1=never to 5=every day). For 2 items (item 10, assessing loss of interest after arousal for women and priapism for men, and item 14, assessing painful orgasm), higher sexual functioning corresponds to lower frequency (eg, 1=every day to 5=never). Items 10 and 14 are included in the total score but not in any subscale score. In addition to providing a total sexual functioning score, the CSFQ-14 allows the possibility of subscale scores: subscales - (i) Desire/Frequency, (ii) Desire/Interest, (iii) Arousal/Excitement, (iv) Orgasm/Completion, (v) Pleasure. SDF is defined as a CSFQ 14 total score at OL Baseline of <=41 for female and <=47 for male participants. Improvement in SF is defined as an increase in the CSFQ-14 total score of ≥3 points.

### 5.3.3. CCI

CCI [redacted]

### 5.3.4. Snaith-Hamilton Pleasure Scale (SHAPS)

The Snaith-Hamilton Pleasure Scale (SHAPS) (Nakonezny 2010, Snaith 1995) is a self-report 14-item, instrument, developed for the assessment of hedonic capacity. It has excellent internal consistency, with construct validity, and is unidimensional in assessing hedonic capacity among adult patients with MDD.

Participants score whether they experience pleasure in performing a list of activities or experiences over the “past few days”. Participants can rate the answers a “definitely/strongly agree”, “agree”, “disagree”

or "strongly disagree". Answers will be rated according to Franken (2007): 1 = "Definitely agree" or "Strongly agree", 2 = "Agree", 3 = "Disagree", and 4 = "Strongly disagree". So, the score of the scale will range from 14 to 56. Negative changes in SHAPS total score indicate improvement.

## 5.4. Safety Analyses

All safety analyses for the different phases will be based on the respective safety analysis set unless otherwise specified:

- OL treatment phase: Safety (OL)
- OL treatment stabilization phase (for specific domains as noted in the relevant sections): Safety (ST)

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.

### 5.4.1. Extent of Exposure

#### 5.4.1.1. Definition

For the OL initial treatment phase and OL stabilization treatment phase, the study intervention duration is defined as (date of last dose of study intervention in the corresponding phase – date of first dose of study intervention in the corresponding phase) + 1. Total number of dosing days is defined as the total number of days the study intervention was administered to the participant (excluding days off study intervention) in the corresponding phase.

For the OL initial treatment phase and OL stabilization treatment phase, the current antidepressant duration is defined as (minimum of end of aticaprant use and end of any antidepressants use in the corresponding phase – maximum of start of aticaprant use and start of any antidepressants use in the corresponding phase) +1.

#### 5.4.1.2. Analysis

For the OL initial treatment phase:

- Descriptive statistics for duration of study intervention and of the current antidepressant (N, mean, SD, median, and range [minimum, maximum]) will be summarized using SAF (OL) analysis set.
- Duration of study intervention will be summarized for the following categories: ≤ 7 days, 8-14 days, 15-21 days, 22-28 days, 29-35 days, 36-42 days, >42 days.

For the OL stabilization treatment phase:

- Descriptive statistics for duration of study intervention and of the current antidepressant (N, mean, SD, median, and range [minimum, maximum]) will be summarized using SAF (ST) analysis set.

- Duration of study intervention will be summarized for the following categories: 0-2 weeks, >2-4 weeks, >4-6 weeks, >6-8 weeks, >8-10 weeks, >10 weeks.

### 5.4.2. Compliance

Compliance will be calculated for the study intervention as:

- Compliance (%) = (number of days when participant took the expected number of tablets in the corresponding phase) / (duration of study intervention in the corresponding phase) x 100%

Compliance of study intervention will be summarized separately for the OL initial treatment phase and OL treatment stabilization phases.

The percent compliance will be categorized (<60%, 60-<80%, 80-<100%, 100%) and the number and percentage of participants in each category will be summarized for study intervention and for the current antidepressant.

### 5.4.3. 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). Any AE occurring at or after the administration of study intervention in OL initial treatment phase through the end of DB treatment maintenance phase is considered to be treatment emergent. If the event occurs on the day of the first dose of administration of study intervention in the OL initial treatment phase and action taken is not entered as 'Not Applicable' in the database, then the event will be considered as 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 in the OL initial treatment phase based on partial onset date or resolution date. All reported 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.

Assignment of adverse events to the appropriate phase will be made based on the following rules:

**OL initial treatment phase:**

AEs during the OL initial treatment phase will satisfy the condition: OL initial treatment phase start date ≤ AE onset date < OL initial treatment end date.

**OL treatment stabilization phase:**

AEs during the OL treatment stabilization phase will satisfy the condition: OL treatment stabilization treatment phase start date ≤ AE onset date < OL stabilization treatment end date.

**DB treatment maintenance phase:**

AEs during the DB phase will satisfy the condition: DB phase start date ≤ AE onset date ≤ DB phase end date.

**Follow-up phase:**

AEs that are assigned to the follow-up phase will not be considered as treatment-emergent. AEs during the follow-up phase will satisfy the condition: follow-up phase start date ≤ AE onset date ≤ follow-up phase end date.

Note that for participants who continue into the DB treatment maintenance phase, in the case where time parts are available for both AE onset date and DB phase start date, the time parts will also be used to determine if an AE is treatment emergent in the OL treatment stabilization phase or DB treatment maintenance phase as follows:

- **OL treatment stabilization phase:** AEs during the OL treatment stabilization phase will satisfy the condition: OL treatment stabilization phase start date ≤ AE onset date/time < DB phase start date/time.
- **DB treatment maintenance phase:** AEs during the DB treatment maintenance phase will satisfy the condition: DB phase start date/time ≤ AE onset date/time ≤ DB phase end date

If the time part is missing in both or in either of the AE onset date and DB treatment maintenance phase start date, the AE that occurs on the DB phase start date will be considered as TEAE for the DB treatment maintenance phase but not for the OL treatment stabilization phase.

Summary tables will be provided respectively for the OL initial treatment phase using SAF (OL) analysis set and for the OL treatment stabilization phase using SAF (ST) analysis set:

- AEs (all AEs, and AEs with incidence of at least 5% in any treatment group)
- Serious AEs (SAEs)
- AEs leading to treatment interruption (not applicable to the follow-up phase)
- AEs leading to discontinuation of study intervention (not applicable to the follow-up phase)
- AEs by severity
- AEs by relationship to study intervention
- Severe AEs
- AEs of special interest
  - CCI [redacted]
  - CCI [redacted]
- AEs of clinical interest
  - GI system organ class AEs
  - GI AEs that were treated with concomitant medications
  - Suicide/Self-injury (First Sub SMQ)
  - AEs suggestive of abuse potential (Appendix 8)

In addition to the summary tables, listings will be provided for participants in OL and DB phase who:

- Died
- Had SAEs
- Had AEs leading to discontinuation of study intervention
- Had AEs of special interest
  - Special interest AEs include CCI [redacted]
- Had AEs of clinical interest
  - GI system organ class AEs along with the treated concomitant medications
  - Suicide/Self-injury (First Sub SMQ)
  - AEs suggestive of abuse potential

In addition, for each AESI, the number of days of dosing prior to onset, duration of the event, frequency distribution of the number of occurrences, and number of participants who were treated with concomitant medications will be summarized.

### 5.4.4. Additional Safety Assessments

#### 5.4.4.1. Clinical Laboratory Tests

Clinical laboratory test values collected in the OL initial treatment, OL treatment stabilization, and DB treatment maintenance phases will be considered "treatment-emergent markedly abnormal" (TEMA) using the criteria relative to baseline (OL) defined by the sponsor listed in Appendix 8.

- If the postbaseline value is above the upper limit of the markedly abnormal criteria and the baseline (OL) value is below the upper limit, then the postbaseline marked abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit of the markedly abnormal criteria with the baseline value being above the lower limit of the markedly abnormal criteria.
- If the baseline (OL) value is missing, a postbaseline marked abnormality will always be considered as TE.

The following analyses will be performed for the chemistry, hematology, and urinalysis laboratory tests, respectively for the entire OL treatment phase:

- Descriptive statistics and the change from baseline (OL) will be summarized at all scheduled time points through the entire OL treatment phase.
- The number and percentage of participants with treatment-emergent markedly abnormal values to study intervention will be presented for the entire OL treatment phase. It will be conducted for all participants and separately for the participants who experience GI TEAEs.
- Incidence of participants with ALT values $\geq$ 3*upper normal limit (ULN), AST values $\geq$ 3*ULN, total bilirubin values $\geq$ 2*ULN, and international normalized ratio (INR) > 1.5 (if measured) will be presented for the entire OL treatment phase.
- Incidence of hepatic toxicity (Hy's Law) defined as ALT or AST values $\geq$ 3*ULN AND alkaline phosphatase < 2*ULN AND total bilirubin values $\geq$ 2*ULN OR international normalized ratio

(INR) > 1.5 (if measured) will be presented for the entire OL treatment phase. Participants with baseline (OL) values meeting these criteria will not be considered as having treatment-emergent hepatic toxicity.

- A listing of participants with markedly abnormal laboratory values relative to baseline (OL) will be provided for the three treatment phases. A listing of participants with ALT ≥ 3* ULN or AST values ≥ 3*ULN) and participants with hepatic toxicity (suspected Hy's Law cases) relative to baseline (OL) in the OL and DB treatment phase will be provided.

#### 5.4.4.2. Vital Signs and Physical Examination Findings

Continuous vital sign parameters including temperature, weight, pulse, blood pressure (systolic and diastolic), and Body Mass Index (BMI) will be summarized at each assessment time point. Body Mass Index will be calculated as weight (kg)/(height (m))$^2$, at each time point that body weight is measured. The height measurement collected at screening will be used in the calculation. Change from the baseline will be summarized over time. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Abnormality criteria (based on criteria defined table 3 below) will be applied to post-baseline values in the three treatment phases. Post-baseline values will be considered treatment-emergent if they meet both value and change criteria:

- Treatment-emergent in the three treatment phases will be concluded if the postbaseline value is above the upper limit and the baseline (OL) 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 (OL) value is missing, a postbaseline abnormality will always be considered as TE.

**Table 3: Clinically Important Abnormalities in Vital Signs**

| Vital Sign | Abnormal Category | Criteria |
|---|---|---|
| Pulse | Abnormally high | ≥100 bpm and with ≥15 bpm increase from baseline |
| | Abnormally low | ≤50 bpm and with ≥15 bpm decrease from baseline |
| Systolic blood pressure | Abnormally high | ≥180 mm Hg and with ≥20 mm Hg increase from baseline |
| | Abnormally low | ≤90 mm Hg and with ≥20 mm Hg decrease from baseline |
| Diastolic blood pressure | Abnormally high | ≥105 mm Hg and with ≥15 mm Hg increase from baseline |
| | Abnormally low | ≤50 mm Hg and with ≥15 mm Hg decrease from baseline |
| Temperature | Abnormally high | >37.5°C |
| | Abnormally low | <35.5°C |
| Weight | Abnormally high | increase ≥7% from baseline |
| | Abnormally low | decrease ≥7% from baseline |

The following analyses will be performed:

- Descriptive statistics and the change from baseline (OL) will be summarized at all scheduled time points through entire OL treatment phase.
- Incidence of treatment-emergent clinically important vital signs relative to baseline (OL), as defined in Table 3, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for the entire OL treatment phase.
- A listing of participants with treatment-emergent clinically important abnormalities relative to baseline (OL) in vital signs during the three treatment phases will be presented, along with a listing of clinical important vital sign measurements.

#### 5.4.4.3. Electrocardiogram

The ECG parameters that will be analyzed are heart rate, PR interval, QRS interval, QT interval, and corrected QT (QTc) interval using the following correction methods: Bazett's formula (QTcB), Fridericia's formula (QTcF).

Bazett's formula: QTcB (msec) = QT (msec) / (RR (msec)/1000)$^{1/2}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/2}$;

Fridericia's formula: QTcF (msec) = QT (msec) / (RR (msec)/1000)$^{1/3}$; if RR is missing, use QT (msec) * (HR(bpm)/60)$^{1/3}$;

Baseline is the most recent assessment prior to the first dose, or average of the most recent assessments prior to the first dose if multiple assessments are done on the same day.

Criteria for abnormal QTc values and abnormal limits for ECG parameters are defined below in Table 4 and Table 5 respectively. Post-baseline values will be considered treatment-emergent if they meet both value and change criteria.

**Table 4: Criteria for Abnormal QTc Values and Changes From Baseline**

| Parameter | Classification | Criteria |
|---|---|---|
| QTc change from baseline | No concern<br>Concern<br>Clear concern | ≤30<br>>30 – <= 60<br>> 60 |
| QTc value | Normal<br><br>> 450 – 480 for male,<br>> 470 – 480 for female<br>> 480 – 500<br>> 500 | ≤450 for male,<br>≤470 for female<br>>450 to ≤480 for male,<br>>470 to ≤480 for female<br>>480 – ≤500<br>> 500 |

Abnormality criteria (based on criteria defined in Table 5) will be applied to baseline (OL) and post-baseline values in the three treatment phases.

Post-baseline abnormalities will be compared with their corresponding baseline (OL) result:

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

**Table 5: Abnormal Limits for ECG Parameters**

| ECG Parameter | Outside of normal limit if ... | |
|---|---|---|
| | Abnormally low | Abnormally high |
| Heart Rate (bpm) | ≤ 50 bpm | ≥100 bpm |
| PR interval (msec) | ≤ 120 msec | ≥ 200 msec |
| QRS interval (msec) | ≤ 60 msec | ≥120 msec |
| QT interval (msec) | ≤ 200 msec | ≥500 msec |
| RR interval (msec) | < 600 msec | > 1200 msec |

The following analyses will be performed for ECG parameters:

- The number and percentage of participants in each QTc value classification will be summarized at each time point for the entire OL treatment phase.

- The number and percentage of participants with QTc interval increases from baseline (OL) to the maximum postbaseline value and each post dose time point will be summarized respectively for the entire OL treatment phase.
- Shift table will be provided from baseline (OL) to maximum post baseline QTc interval for the entire OL treatment phase.
- Descriptive statistics of ECG parameters and change from baseline (OL) will be summarized at each scheduled time point for the entire OL treatment phase.
- The number and percentage of participants with treatment-emergent ECG values outside predefined limits relative to baseline (OL) will be presented for the entire OL treatment phase.

#### 5.4.4.4. Other Safety Parameters

##### 5.4.4.4.1. Columbia Suicide Severity Rating Scale (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.

| **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 |

At each time point, an event of suicidal ideation or behavior will be assigned a score of 1 to 10 based on the maximum response for the C-SSRS at that visit. If there is no event of suicidal ideation or behavior, 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 an event of non-suicidal self-injurious behavior only will not be considered as having suicidal ideation or behavior, therefore a score of 0 will be assigned. However, an

additional score of 11 will be assigned to summarize any participants with an event of non-suicidal self-injurious behavior.

Shifts from the baseline (OL) to the maximum postbaseline score pertaining to suicidal ideation or suicidal behavior (i.e., scores 1 to 10) will be summarized for the entire OL treatment phase using SAF (OL) set.

The maximum score (of scores 0 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). Shifts from baseline (OL) to the maximum postbaseline category will be summarized for the entire OL treatment phase using SAF (OL) set.

A frequency distribution of the scores for the 11 categories (0 to 10), as well as the number and proportion of participants with non-suicidal self-injurious behavior (a score of 11) will be provided for the entire OL treatment phase using SAF (OL) set.

A listing of potentially suicidal ideation, suicidal behavior, or non-suicidal self-Injurious behavior will be provided for subjects who had at least one event during the study.

## 5.5. Other Analyses

### 5.5.1. Pharmacokinetics

No PK analyses will be performed for this study.

### 5.5.2. Biomarkers

No analysis of biomarker data will be performed for this study.

### 5.5.3. Definition of Subgroups

No subgroup analyses will be performed for this study.

## 5.6. Interim Analyses

To evaluate the assumptions used in the sample size calculation, relapse rates will be monitored sequentially during the DB treatment maintenance phase. Depending on the recruitment rate and the observed relapse rates in the study, an IA may be performed on the FAS_IA, which includes all participants who have achieved stable response at the end of the OL treatment stabilization phase and who receive at least 1 dose of study intervention during the DB treatment maintenance phase at the time of the IA data cutoff. The IA will be performed after approximately a total of 60 relapse events (of the 127 maximum) are observed in stable responders. The intent of the IA is to perform event re-estimation. Adjustments made to the required number of events will not be revealed to the study team. Treatment difference will be compared using a log-rank test. A futility analysis may be conducted at the IA. Details will be specified in the IA SAP, which will be finalized before interim database lock.

However, as the study was terminated, the interim analyses are not applicable for this study.

### 5.6.1. Independent Data Monitoring Committee (IDMC)

Not applicable as the study was terminated.

# 6. SUPPORTING DOCUMENTATION

## 6.1. Appendix 1 List of Abbreviations

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse event(s) of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| ATC | Anatomic and therapeutic class |
| BMI | Body mass index |
| CSFQ-14 | Sexual Functioning Questionnaire - short-form |
| C-SSRS | Columbia suicide severity rating scale |
| CRF | Case report form |
| CCI | [redacted] |
| DB | Double-blind |
| ECG | Electrocardiogram |
| EU | European union |
| FU | Follow-up |
| GI | Gastrointestinal |
| ICH | International Conference on Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IQ | Interquartile |
| LS | Least squares |
| MADRS | Montgomery-asberg depression rating scale |
| MDD | Major depressive disorder |
| MDD ANH+ | MDD with moderate-to-severe anhedonia |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NSAIDs | Non-steroidal anti-inflammatory drugs |
| OL | Open label |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SHAPS | Snaith-Hamilton Pleasure Scale |
| SMQ | Standardized MedDRA Query |
| SNRI | Selective norepinephrine reuptake inhibitors |
| SSRI | Selective serotonin reuptake inhibitor |
| TE | Treatment emergent |

## 6.2. Appendix 2 Changes to Protocol-Planned Analyses

As the study 67953964MDD3005 is prematurely terminated, the final analyses will be conducted descriptively, focusing on the safety data. No efficacy analyses will be conducted. No hypothesis testing will be performed.

## 6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group and overall. In addition, the distribution of participants by region, country/territory, and site ID will be presented unless otherwise noted.

Table 6 presents a list of the demographic variables at baseline (OL) that will be summarized for the SAF (OL) analysis set.

**Table 6: Demographic Variables**

| **Continuous Variables** | **Summary Type** |
|---|---|
| Age (years) | Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and |
| Weight (kg) | |
| Height (cm) | |
| Body Mass Index (BMI) (kg/m$^2$) | |
| **Categorical Variables** | Frequency distribution with the number and percentage of participants in each category. |
| Age group: 18-44, 45-64 | |
| Sex (male, female, unknown, undifferentiated) | |
| Race[a] (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Not Reported) | |
| Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown) | |
| Country/territory | |
| Region (South America, North America, Europe, other) | |
| BMI (underweight <18.5 kg/m$^2$, normal 18.5-<25 kg/m$^2$, overweight 25-<30 kg/m$^2$, obese 30-<40 kg/m$^2$, morbidly obese >=40 kg/m$^2$) | |
| Employment status (any type of employment, any type of unemployment, other) [b] | |
| History of Tabacco use (Yes, No) | |
| History of Cannabis use (Yes, No) | |
| Oral contraceptive use at OL baseline (Yes, No) | |

[a] If multiple race categories are indicated, the Race is recorded as 'Multiple'

[b] Any type of employment includes: any category containing “Employed”, Sheltered Work, Housewife or Dependent Husband, and Student; any type of unemployment includes: any category containing “Unemployed”; Other includes: Retired and No Information Available.

Table 7 presents a list of the disease characteristics variables at baseline (OL) that will be summarized for the SAF (OL) analysis set.

**Table 7: Psychiatric History at Baseline**

| **Continuous Variables** | **Summary Type** |
|---|---|
| Age (years) when diagnosed with MDD | Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]). |
| Duration (weeks) of current depressive episode | |
| Baseline MADRS total score | |
| Baseline CSFQ-14 total score (applicable for FAS_SF analysis set only) | |
| Baseline SHAPS total score | |
| Baseline CCI total score | |
| **Categorical Variables** | Frequency distribution with the number and percentage of participants in each category. |
| Current antidepressant type (SSRI/SNRI) | |
| Number of previous prior antidepressants (0, 1, 2, 3, >3) | |
| Presence of GI Medical History (Yes, No) | |
| Screening C-SSRS category (no event, suicidal ideation, suicidal behavior) | |

* Clinician's assessment of severity of anhedonia is based on clinical evaluation and judgment of impact on the anhedonia domains: interest, motivation, engagement/effort and enjoyment/pleasure.

## 6.4. Appendix 4 Protocol Deviations

In general, the following list of 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 and the participants with major protocol deviations will be summarized by category for SAF analysis set.

- Developed withdrawal criteria but not withdrawn.
- Entered but did not satisfy criteria.
- Received a disallowed concomitant treatment.
- Received wrong treatment or incorrect dose.
- Other

Number of participants not meeting inclusion criteria, or meeting exclusion criteria will be summarized by study intervention group for the safety analysis set.

## 6.5. Appendix 5 Prior and Concomitant Medications

Prior medications 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 on after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC level 2 and level 4 terms and base preferred term for the entire OL phase using SAF (OL) analysis set. 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 summarized. See Appendix 6, Medications of Special Interest for list of categories of medications of special interest.

Prior antidepressant medications will be summarized by ATC level 2 and level 4 terms and base preferred term for the SAF(OL) analysis set.

## 6.6. Appendix 6 Medications of Special Interest

Categories for medications of special interest are defined as follows:

| **Medications of Special Interest Category** |
|---|
| Antidepressants |
| Hypnotic/sedative including z-drugs |
| Treatment for stomach ulcer: Ulcer Proton Pump Inhibitors; H2-receptor antagonists; Antacids and alginates |
| Non-steroidal anti-inflammatory drugs (NSAIDs) |
| Medications for treatment of [redacted] |
| Medications for treatment of [redacted] |

## 6.7. Appendix 7 Criteria for Treatment-emergent Markedly Abnormal Laboratory Values

| Laboratory Parameter | Unit | Low | High |
|---|---|---|---|
| **Clinical Chemistry** | | | |
| Albumin | g/dL | 2.4 | 6.0 |
| Albumin | g/L | 24 | 60 |
| Alkaline phosphatase | U/L | N/A | 250 |
| Alanine transaminase (SGPT) | U/L | N/A | 200 |
| Aspartate transaminase (SGOT) | U/L | N/A | 250 |
| Bicarbonate | mEq/L | 15.1 | 34.9 |
| Bicarbonate | mmol/L | 15.1 | 34.9 |
| Bilirubin (direct) | mg/dL | N/A | 3.0 |
| Bilirubin (direct) | µmol/L | N/A | 51.3 |
| Bilirubin (total) | mg/dL | N/A | 3.0 |
| Bilirubin (total) | µmol/L | N/A | 51.3 |
| Blood urea nitrogen | mg/dL | N/A | 50 |
| Blood urea nitrogen | mmol/L | N/A | 17.9 |
| Calcium | mg/dL | 6 | 12 |
| Calcium | mmol/L | 1.497 | 2.994 |
| Chloride | mEq/L or mmol/L | 94 | 112 |
| Cholesterol | mg/dL | N/A | 300 |
| Cholesterol | mmol/L | N/A | 7.758 |
| Creatine kinase | U/L | N/A | 990 |
| Creatinine | mg/dL | N/A | 3 |
| Creatinine | µmol/L | N/A | 265.2 |
| Gamma glutamyl transferase | U/L | N/A | 300 |
| Glucose Plasma | mg/Dl | 40 | 300 |
| Glucose Plasma | mmol/L | 2.204 | 16.653 |
| Hemoglobin A1c | Fraction of 1 | 0.04 | 0.08 |
| High-density lipoprotein cholesterol (HDL) | mg/dL | 35 | N/A |
| High-density lipoprotein cholesterol (HDL) | mmol/L | 0.905 | N/A |
| Low-density lipoprotein cholesterol (LDL) | mg/dL | 89 | 160 |
| Low-density lipoprotein cholesterol (LDL) | mmol/L | 2.3015 | 4.1376 |
| Phosphate | mg/dL | 2.2 | 8.1 |
| Phosphate | mmol/L | 0.71038 | 2.61549 |
| Potassium | mmol/L | 3.0 | 5.8 |
| Sodium | mEq/L | 125 | 155 |
| Sodium | mmol/L | 125 | 155 |
| Total protein | g/L | 50 | N/A |
| Triglycerides | mg/dL | N/A | 500 |
| Triglycerides | mmol/L | N/A | 5.645 |
| Uric acid | mg/dL | 1.5 | 10 |
| Uric acid | µmol/L | 89.22 | 594.8 |

| | | | |
|---|---|---|---|
| **Hematology** | | | |
| Hematocrit - female | % | 0.28 | 0.50 |
| - male | % | 0.24 | 0.55 |
| Hemoglobin | g/dL | 8 | 19 |
| Hemoglobin | g/L | 80 | 190 |
| Neutrophils | % | 30 | 90 |
| Monocytes | % | N/A | 20 |
| Eosinophils | % | N/A | 10 |
| Basophils | % | N/A | 6 |
| Lymphocytes | % | 10 | 60 |
| Reticulocytes | % | 0.5 | 1.5 |
| Platelet count | $10^9$/L; giga/L | 100 | 600 |
| Red blood cell (RBC) count - female | $10^{12}$/L; tera/L | 3.0 | 5.5 |
| - male | $10^{12}$/L; tera/L | 3.0 | 6.4 |
| White blood cell (WBC) count | $10^9$/L; giga/L | 2.5 | 15.0 |
| **Urinalysis** | | | |
| Urine pH | | N/A | 6.5 |
| Urine specific gravity | | < 1.001 | > 1.035 |

Note: Values should be flagged as markedly abnormally low if the value is less than the value indicated in the "Low" column. Likewise, values should be flagged as markedly abnormally high if the value is greater than the value indicated in the "High" column.

Note: The same limits apply to both males and females unless gender is indicated.

N/A = Not applicable

## 6.8. Appendix 8 AE Suggested to Abuse Potential (PTs)

Potential abuse-related AEs are defined as below:

- SMQ - "Drug Abuse, Dependence and Withdrawal"
- SMQ - "Psychosis and Psychotic Disorders"
- MedDRA preferred terms (PTs):

  Aggression; Confusional state; Decreased activity; Dependence; Disorientation; Dissociation; Dissociative disorder; Dizziness; Drug abuse; Drug abuser; Drug dependence; Drug detoxification; Drug diversion; Drug rehabilitation; Drug tolerance; Drug tolerance increased; Drug use disorder; 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, synaesthetic; 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

- Standardized MedDRA Query (SMQ) and Custom MedDRA Query (CMQ) analyses:

  Dopamine dysregulation syndrome; Drug abuse; Drug abuser; Drug dependence; Drug dependence, antepartum; Drug dependence, postpartum; Drug use disorder; Drug use disorder, antepartum; Drug use disorder, postpartum; Intentional overdose; Intentional product misuse; Maternal use of illicit drugs; Neonatal complications of substance abuse; Substance abuse; Substance abuser; Substance dependence; Substance use disorder; Accidental overdose; Dependence; Disturbance in social behaviour; Drug detoxification; Drug diversion; Drug level above therapeutic; Drug level increased; Drug screen; Drug screen positive; Drug tolerance; Drug tolerance decreased; Drug tolerance increased; Intentional product use issue; Medication overuse headache; Narcotic bowel syndrome; Needle track marks; Overdose; Prescription drug used without a prescription; Prescription form tampering; Reversal of opiate activity; Substance use; Substance-induced mood disorder; Substance-induced psychotic disorder; Toxicity to various agents; Drug withdrawal convulsions; Drug withdrawal headache; Drug withdrawal maintenance therapy; Drug withdrawal syndrome; Drug withdrawal syndrome neonatal; Drug rehabilitation; Rebound effect; Steroid withdrawal syndrome; Withdrawal arrhythmia; Withdrawal catatonia; Withdrawal syndrome; Behavioural addiction; Intentional device use issue; Anti-androgen withdrawal syndrome; Intentional device misuse; Product administered at inappropriate site; Alcohol use disorder; Performance enhancing product use; Intentional misuse of drug delivery system; Cholinergic rebound syndrome; Steroid dependence; Cannabinoid hyperemesis syndrome; Delusion of parasitosis; Behavioral addiction

Note: Some of the PTs listed above are included in the *Drug Abuse, Dependence and Withdrawal*, and *Psychosis and Psychotic Disorders* SMQs

## 6.9. Appendix 9 Quality Tolerance Limits (QTLs)

Quality Tolerance Limit (QTL) parameters and thresholds are defined and will be monitored in in this study. QTL parameters will be summarized. More details are described in the Integrated Analytic Risk-Based Monitoring (iARBM) Plan.

# 7. REFERENCES

1. Franken IH, Rassin E, Muris P. The assessment of anhedonia in clinical and non-clinical populations: further validation of the Snaith-Hamilton Pleasure Scale (SHAPS). J Affect Disord. 2007;99(1-3):83-89.
2. Keller A, McGarvey EL, Clayton AH. Reliability and construct validity of the Changes in Sexual Functioning Questionnaire short-form (CSFQ-14). J Sex Marital Ther. 2006;32(1):43-52.
3. Investigator's Brochure: JNJ-67953964 (aticaprant), edition 6. Janssen Research & Development (20 Jan 2022)McKenna SP (1992),
4. Khin NA. Update on FDA exploratory analyses of aggregated efficacy data from antidepressant trials. Presented at NCDEU Regulatory Plenary. New FDA & EMA initiatives in Alzheimer's disease, depression and schizophrenia. May 30, 2013
5. Nakonezny PA, Carmody TJ, Morris DW, Kurian BT, Trivedi MH. Psychometric evaluation of the Snaith– Hamilton Pleasure Scale (SHAPS) in adult outpatients with major depressive disorder. Int Clin Psychopharmacol 2010;25(6):328-333.
6. CCI [redacted]
7. Snaith RP, Hamilton M, Morley S, Humayan A, Hargreaves D, Trigwell P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. Br J Psychiatry. 1995;167(1):99-103.