Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-blind, Multicenter, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Aticaprant 10 mg as Adjunctive Therapy in Adult Participants with Major Depressive Disorder (MDD) with Moderate-to-severe Anhedonia and Inadequate Response to Current Antidepressant Therapy and an Open-label Long-term Extension Treatment with Aticaprant

Protocol 67953964MDD3007; Phase 3

JNJ-67953964 (Aticaprant)

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

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TABLE OF CONTENTS

TABLE OF CONTENTS 2
1. INTRODUCTION 5
1.1. Objectives and Endpoints 5
1.2. Study Design 7
1.3. Intervention Allocation 10
2. STATISTICAL HYPOTHESES 10
3. SAMPLE SIZE DETERMINATION 10
4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS 11
5. STATISTICAL ANALYSES 12
5.1. General Considerations 12
5.1.1. Analysis Phases 12
5.1.2. Visit Windows 13
5.1.3. Imputation of Efficacy 18
5.1.4. Study intervention groups 18
5.2. Participant Dispositions 19
5.3. Primary Endpoint(s) Analysis 19
5.3.1. Definition 19
5.3.2. Analysis Methods 20
5.4. Secondary Endpoint(s) Analysis 20
5.4.1. Key Secondary Endpoint 1 20
5.4.1.1. CCI [redacted] (CCI [redacted] 20
5.4.1.1.1. Definition 20
5.4.1.1.2. Analysis Methods 21
5.4.2. Key Secondary Endpoint 2 21
5.4.2.1.1. Definition 21
5.4.2.1.2. Analysis Methods 21
5.6. Safety Analyses 22
5.6.1. Extent of Exposure 22
5.6.1.1. Definition 22
5.6.1.2. Analysis 22
5.6.1.3. Compliance 24
5.6.2. Adverse Events 24
5.6.3. Additional Safety Assessments 26
5.6.3.1. Clinical Laboratory Tests 26
5.6.3.2. Vital Signs and Physical Examination Findings 27
5.6.3.3. Electrocardiogram 28
5.6.3.4. Other Safety Parameters 30
5.6.3.4.1. Columbia Suicide Severity Rating Scale (C-SSRS) 30
5.7. Other Analyses 31
5.7.1. Pharmacokinetics 31
5.7.2. Biomarkers 31
5.7.3. Definition of Subgroups 31
5.8. Interim Analyses 32
5.8.1. Independent Data Monitoring Committee (IDMC) 32
6. SUPPORTING DOCUMENTATION 33
6.1. Appendix 1 List of Abbreviations 33
6.2. Appendix 2 Changes to Protocol-Planned Analyses 34
6.3. Appendix 3 Demographics and Baseline Characteristics 35
6.4. Appendix 4 Protocol Deviations 37
6.5. Appendix 5 Prior and Concomitant Medications 38
6.6. Appendix 6 Medications of Special Interest 39
6.7. Appendix 7 Criteria for Treatment-emergent Markedly Abnormal Laboratory Values 40

6.8. Appendix 8 AE Suggested to Abuse Potential (PTs) 42
6.9. Appendix 9 Quality Tolerance Limits (QTLs) 43
7. REFERENCES 44

VERSION HISTORY

Table – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1.0	25Sep2024	Not Applicable	Initial release
2.0	10Oct2024	Timing of database lock, unblinding and planned analyses was added in section 1	For clarification
		Justification for stratification factor and model inclusion for the primary estimand analysis was added in section 5.3.2.1.1	Add per health authority request
		"Family history of Tabacco use" was updated to be "History of Tabacco usage" in section 6.3	Typo correction and to be consistent with the eCRF data collection
		Editorial changes in multiple sections	Clarifications or fixing typos
3.0	26 June 2025	Definition of Open-Label Treatment Phase Start Data/Time was added in section 5.1.1	For clarification
		Visit Window was updated in section 5.1.2 for Hematology, Chemistry and Urinalysis OL phase	Correction for miscalculated visit window
		Added descriptive summary for the CSFQ-14 total score by SEX	To present summary score of this questionnaire by version for sex (female and male)
		A condition "or through the end of OL phase if the participants continue to OL treatment phase" was added to the treatment-emergent definition "Any AE occurring at or after the initial administration of study intervention through the end of DB phase is considered to be treatment emergent." in section 5.6.2	For clarification
		Removed the following analyses: - Hypothesis testing and estimand language for primary and key secondary endpoints - Multiplicity adjustment - Analyses for other secondary and exploratory endpoints - Subgroup analyses and psychiatry disease characteristics which are not needed for the abbreviated CSR - PK and biomarker analyses	This study was prematurely terminated due to sponsor's decision. The final analyses will be conducted descriptive for all safety data and partial efficacy data limited to primary and key secondary endpoints. 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 67953964MDD3007 study was prematurely terminated. This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all necessary analyses for the abbreviated CSR for the study 67953964MDD3007, including all safety data and partial efficacy data limited to the primary and key secondary endpoints. Analyses of other secondary and exploratory endpoints stated in the protocol will not be performed unless otherwise specified.

Analyses for both the double-blind (DB) phase and open-label (OL) phase are described. The database lock and unblinding will occur after the last participant completes study participation.

1.1. Objectives and Endpoints

This is a randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy, safety, and tolerability of aticaprant 10 mg as adjunctive therapy in adult participants with major depressive disorder (MDD) with moderate-to-severe anhedonia and inadequate response to current antidepressant therapy and an open label long-term extension treatment with aticaprant.

OBJECTIVES AND ENDPOINTS

Due to study termination analyses pertaining to the following objectives stated in the protocol will not be performed: other 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.

Double-Blind Treatment Phase

Objectives	Endpoints
Primary	
• To evaluate the efficacy of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in adult participants with MDD with moderate-to-severe anhedonia (ANH+) who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI.	• Change from baseline (ie, Day 1 pre-randomization, and hereafter referred to as 'baseline') to Day 43 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.
Key Secondary To evaluate the efficacy of adjunctive aticaprant 10 mg compared with placebo in adult participants with MDD ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI on the following:	
• Anhedonia symptoms (patient-reported)	• Change from baseline to Day 43 in CCI [redacted] (CCI [redacted] total score.
• Sexual function (patient-reported) in the subset of participants with sexual dysfunction (defined as CSFQ-14 total score ≤41 for female, or ≤47 for male) at baseline	• Change from baseline to Day 43 in Changes in Sexual Function Questionnaire – 14 items (CSFQ-14) total score.

Objectives	Endpoints
Safety Safety will be assessed for all participants.	
• To assess the safety and tolerability of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant (SSRI/SNRI) in participants with MDD ANH+	• Adverse events (AE) including AEs of special interest (AESIs) • Vital signs including weight, body mass index (BMI) • Suicidality assessment using the C-SSRS • Laboratory values and ECGs

Open-Label Treatment Phase

Objectives	Endpoints
Safety Safety will be assessed for all participants	
• To assess the long-term safety and tolerability of aticaprant 10 mg as adjunctive therapy to an antidepressant (SSRI/SNRI) in participants with MDD ANH+	• Adverse events (AE) including AEs of special interest (AESIs). • Vital signs including weight, body mass index (BMI). • Suicidality assessment using the C-SSRS. • Laboratory values and ECGs.

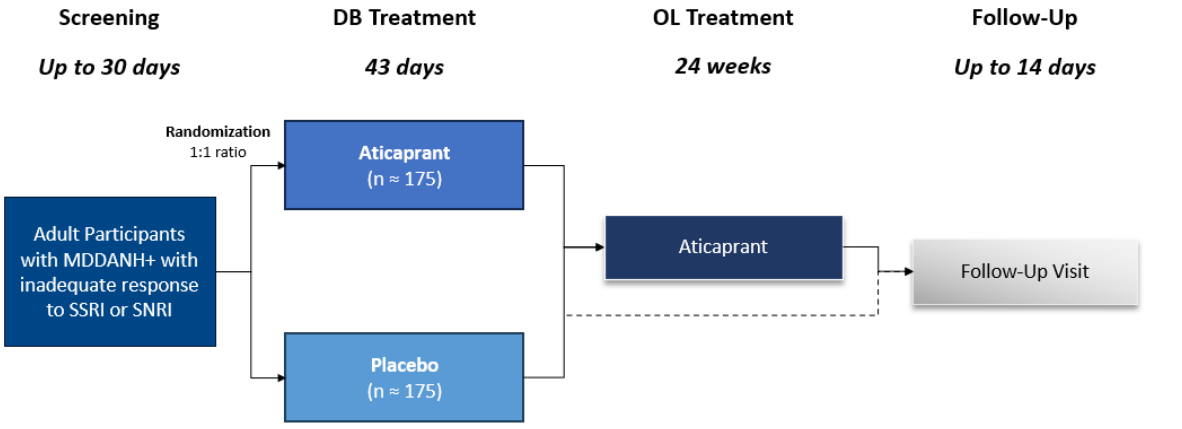
1.2. Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, interventional Phase 3 study to assess the efficacy, safety, and tolerability of aticaprant 10 mg as adjunctive therapy in adult participants (18 to 64 years) with MDD ANH+ who have had an inadequate response to a SSRI or SNRI antidepressant in the current depressive episode. Following completion of the DB Treatment Phase, participants may continue in an OL Treatment Phase of up to 24 weeks.

This study will consist of the following phases:

- Eligibility screening phase (up to 30 days prior to first dose administration)
- DB Treatment Phase (43 days)
- OL Treatment Phase (24 weeks)
- Follow-up Phase (up to 14 days)

Figure 1: Schematic Overview of the Study



Notes:
- All participants will continue to take their current SSRI or SNRI (only 1) antidepressant therapy (at the same dose, every day, and at approximately the same time of the day as prior to entering the study) in the DB Treatment Phase. Throughout the OL Treatment Phase, participants will receive adjunctive aticaprant along with their standard-of-care antidepressant therapy. It is recommended that participants continue the same SSRI/SNRI antidepressant therapy taken during the DB Treatment Phase. Changes to the current antidepressant therapy are allowed (per investigator's discretion) in the OL Treatment Phase.

Abbreviations: ANH+ = with mpoderate-to-severe anhedonia; DB = Double-Blind; MDD = Major Depressive Disorder; OL = Open-Label; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor

Abbreviations: ANH+ = with 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 study population will include adults, aged 18 to 64 years (inclusive) who meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for recurrent or single episode MDD, without psychotic features, based upon clinical assessment and confirmed by the Structured Clinical Interview for DSM-5 Axis I Disorders - Clinical Trials Version (SCID-CT). Participants must have symptoms of anhedonia based on clinical assessment and confirmed by presence of anhedonia (positive response to major depressive episode [MDE] module symptom Item 2) on the SCID-CT at screening and a Snaith-Hamilton Pleasure Scale (SHAPS) total score of ≥[redacted] at screening and baseline visits. At the start of screening, all participants must have had an inadequate response to at least 1 and up to 5 (inclusive) oral antidepressant treatments, administered at an adequate dose (at or above the minimum therapeutic dose per Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [MGH ATRQ]) and duration (at least 6 weeks) in the current episode of depression. An inadequate response is defined as <50% reduction in depressive symptom severity as assessed by the MGH ATRQ, but with some improvement (>0%). This assessment of response must apply to the participant's current SSRI/SNRI antidepressant treatment. Additionally, participants must have moderate-to-severe depression with MADRS total score ≥25 during screening and baseline without a clinically significant improvement (ie, an improvement of more than 25% on their MADRS total score) between the screening and the baseline site-rater assessments. A Site Independent Qualification Assessment (SIQA) will assess the validity of the participants' current MDE, overall symptom severity, and antidepressant treatment response for inclusion in the study.

Participants will be randomized in the DB Treatment Phase in a 1:1 ratio to receive 10 mg of adjunctive aticaprant or adjunctive placebo. The study intervention will be administered orally as a film-coated tablet to be taken once daily.

Throughout the Screening and DB Treatment Phases, all participants will continue their current SSRI/SNRI antidepressant therapy at the same dose as prior to entering the Screening and DB Treatment Phase.

Participants are considered to have completed the DB Treatment Phase of the study if they complete the Day 43 Visit of the DB Treatment Phase (Visit 2.6), including the MADRS assessment at the end of the 6-week DB Treatment Phase (ie, Day 43 MADRS) and have not discontinued study intervention early during the DB Treatment Phase.

Participants who have completed the DB Treatment Phase as defined above and have been compliant to the study intervention may participate in a 24-week OL Treatment Phase. The investigator needs to assess and confirm in source documentation that, based on clinical judgment, it is in the participant's best interest to participate in this phase.

During the OL Treatment Phase, all participants will receive OL aticaprant 10 mg once daily.

Participants are considered to have completed the OL Treatment Phase if they complete the Week 31 Visit of the OL Treatment Phase (Visit 3.7) and have not discontinued study intervention during the OL Treatment Phase.

Participants not entering the OL Treatment Phase will be considered to have completed the study if they complete Visit 2.6 in the DB Treatment Phase and have not discontinued study intervention early during the DB Treatment Phase, and the Follow-up Phase (Visit 4.1).

Participants entering the OL Treatment Phase will be considered to have completed the study if they complete Visits 2.6 and 3.7 in the DB Treatment Phase and OL Treatment Phase, respectively, and have not discontinued study intervention during the OL Treatment Phase and the Follow-up Phase (Visit 4.1).

The end of study is considered as the last scheduled study assessment for the last participant in the study.

1.3. Intervention Allocation

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups based on a computer-generated randomization schedule implemented in the IWRS before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified by sexual dysfunction (SF) status (presence vs absence of sexual dysfunction [SDF] at DB baseline), sex, and country/territory. The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Presence of SDF (SDF+) is defined as CSFQ 14 total score at DB Baseline of <= 41 for female and <= 47 for male participants. Absence of SDF (SDF-) is defined as CSFQ 14 total score at DB Baseline of >41 for female and >47 for male participants.

2. STATISTICAL HYPOTHESES

As the study is prematurely terminated, no hypotheses will be specified. All analyses conducted will be exploratory. No multiplicity adjustments will be made for the efficacy endpoints.

3. SAMPLE SIZE DETERMINATION

Approximately 350 participants were to be enrolled in the study. Participants entering the DB Treatment Phase will be randomized in a 1:1 ratio to adjunctive aticaprant 10 mg or adjunctive placebo. CCI

CCI

However, the study will be terminated before the required number of 350 participants have been enrolled.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

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

Population	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who were randomized in the study
Full Analysis Set (DB) – FAS (DB)	All randomized participants who took take at least 1 dose of the study intervention in the DB Treatment Phase
Full analysis Set-Sexual Functioning (DB) – FAS_SF (DB)	All randomized participants with SDF at DB baseline who take at least 1 dose of study intervention in the DB Treatment Phase
Safety (DB)	All randomized participants who take at least 1 dose of study intervention in the DB Treatment Phase.
Full Analysis Set (OL) – FAS (OL)	All participants who take at least 1 dose of study intervention in the OL Treatment Phase
Safety (OL)	All participants who take at least 1 dose of study intervention in the OL treatment phase
Follow-up analysis set	All participants who entered the follow-up (FU) phase after DB treatment phase or OL treatment phase on or before the data cut-off date.

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 DB phase.

Double-Blind Treatment Phase

The analysis reference start date of the double-blind treatment phase (DB phase start date) is the date of the first dose of double-blind study intervention. For participants who continue to the OL treatment phase, the analysis reference end date of the DB treatment phase (DB treatment phase end date) is the date when the study medication was started in the OL treatment phase. For participants who don't continue to the OL treatment phase, the analysis reference end date is the maximum of the date of the last visit in the double-blind treatment phase and date of completion or early withdrawal from the double-blind treatment phase.

For randomized participants who did not receive any study intervention in the double-blind treatment phase, both analysis reference start and end dates are missing for the double-blind treatment phase.

OL Treatment Phase

Start and end dates of the open-label treatment phase are only defined for participants who participated in the open-label treatment phase. The analysis reference start date of the OL treatment phase is the day of the first dose of study intervention in the OL treatment phase (OL treatment phase start date). The analysis reference end date of the OL treatment phase (OL treatment phase end date) is the maximum of the date of the last visit in the OL treatment phase and date of completion or early withdrawal from the OL treatment phase. In cases where the DB end date is equal to the OL start date, time will be used when available to correctly allocate analysis records to their respective phases. If time cannot be used, the data will be allocated to the OL phase for adverse event data, and to the DB phase for all other domains.

Follow-up (FU) Phase

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

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 Visit Number	Time Interval (label on output)	Time Interval (Day)*	Target Time Point (Day)*
MADRS	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.3	Day 15 (DB)	2 to 22	15
		2.5	Day 29 (DB)	23 to 36	29
		2.6	Day 43 (DB)	37 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
	OL	3.1	Baseline (OL)	<=1	
		3.2	Week 4 (OL)	2 to 56	29
		3.4	Week 12 (OL)	57 to 113	85
		3.6	Week 20 (OL)	114 to 155	141
		3.7	Week 24 (OL)	156 to End of OL	169
		OL final visit	Endpoint (OL)	2 to End of OL	
	FU	4.1	Follow-up (DB)	End of DB + 1 to End of FU	7-14
		4.2	Follow-up (OL)	End of OL + 1 to End of FU	7-14
CCI CSFQ-14	DB	2.1	Baseline (DB)	<=1	1
		2.3	Day 15 (DB)	2 to 22	15
		2.5	Day 29 (DB)	23 to 36	29
		2.6	Day 43 (DB)	37 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	43
	OL	3.1	Baseline (OL)	<=1	
		3.2	Week 4 (OL)	2 to 56	29
		3.4	Week 12 (OL)	57 to 113	85
		3.6	Week 20 (OL)	114 to 155	141
		3.7	Week 24 (OL)	156 to End of OL	169
		OL final visit	Endpoint (OL)	2 to End of OL	

	FU	4.1	Follow-up (DB)	End of DB + 1 to End of FU	7-14
		4.2	Follow-up (OL)	End of OL + 1 to End of FU	7-14
Vital Signs	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.6	Day 43 (DB)	2 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	43
	OL	3.1	Baseline (OL)	<=1	
		3.2	Week 4 (OL)	2 to 79	29
		3.7	Week 24 (OL)	80 to End of OL	169
		OL final visit	Endpoint (OL)	2 to End of OL	
	FU	4.1	Follow-up (DB)	End of DB + 1 to End of FU	7-14
		4.2	Follow-up (OL)	End of OL + 1 to End of FU	7-14
ECG	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.6	Day 43 (DB)	2 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
	OL	3.1	Baseline (OL)	<=1	
		3.7	Week 24 (OL)	2 to End of OL	169
		OL final visit	Endpoint (OL)	2 to End of OL	
	FU	4.1	Follow-up (DB)	End of DB + 1 to End of FU	7-14
		4.2	Follow-up (OL)	End of OL + 1 to End of FU	7-14
Hematology, Chemistry Urinalysis	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.6	Day 43 (DB)	2 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	43
	OL	3.1	Baseline (OL)	<=1	
		3.3	Week 8 (OL)	End of DB + 1 to 85	57
		3.5	Week 16 (OL)	86 to 141	113
		3.7	Week 24 (OL)	142 to End of OL	169
		OL final visit	Endpoint (OL)	2 to End of OL.	

	FU	4.1	Follow-up (DB)	End of DB + 1 to End of FU	7-14
		4.2	Follow-up (OL)	End of OL + 1 to End of FU	7-14
C-SSRS	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.2	Day 8	2 to 11	8
		2.3	Day 15	12 to 18	15
		2.4	Day 22	19 to 25	22
		2.5	Day 29	26 to 36	29
		2.6	Day 43	37 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
	OL	3.1	Baseline (OL)	<=1	
		3.2	Week 4 (OL)	2 to 43	29
		3.3	Week 8 (OL)	44 to 71	57
		3.4	Week 12 (OL)	72 to 99	85
		3.5	Week 16 (OL)	100 to 127	113
		3.6	Week 20 (OL)	128 to 155	141
		3.7	Week 24	156 to End of OL.	169
		OL final visit	Endpoint (OL)	2 to End of OL	
	FU	4.1	Follow-up (DB)	End of DB + 1 to End of FU	7-14
		4.2	Follow-up (OL)	End of OL + 1 to End of FU	7-14
Weight/BMI	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.6	Day 43	2 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	43
	OL	3.1	Baseline (OL)	<=1	
		3.4	Week 12 (OL)	2 to 127	85
		3.7	Week 24 (OL)	128 to End of OL	169
		OL final visit	Endpoint (OL)	2 to End of OL	
	FU	4.1	Follow-up (DB)	End of DB + 1 to End of FU	7-14
		4.2	Follow-up (OL)	End of OL + 1 to End of FU	7-14

*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 items)

5.1.4. Study intervention groups

All summaries for DB phase will be presented by study intervention group “Aticaprant+AD” and “Placebo+AD”. Summaries for the OL phase will be displayed by treatment sequence “Aticaprant+AD/Aticaprant+AD” and “Placebo+AD/Aticaprant+AD” and total.

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 throughout the DB phase by intervention group and overall for the all randomized and FAS (DB) analysis sets:

- Participants randomized
- Participants who received DB study intervention
- Participants who completed, discontinued and reasons for discontinuation of study intervention during DB phase
- Participants who completed DB treatment and entered OL phase
- Participants who completed DB treatment and directly entered FU phase
- Participants who completed, terminated and reasons for discontinuation of study without entering the OL phase.

The number of participants in the following disposition categories will be summarized throughout the OL phase by intervention group and overall for the Safety (OL) analysis set:

- Participants who received OL study intervention
- Participants who completed, discontinued and reasons for discontinuation of study intervention during OL phase
- Participants who completed, terminated and reasons for discontinuation of study

The number of participants in each analysis set will be provided.

Listings of participants will be provided for the following categories:

- Participants who discontinued DB or OL study intervention
- Participants who were unblinded during the DB phase
- Participants who were randomized yet did not receive study intervention.

5.3. Primary Endpoint(s) Analysis

5.3.1. Definition

The primary efficacy endpoint is the change from baseline in MADRS total score at Day 43 in FAS (DB).

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, 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. Imputation of total score is presented in Section 5.1.3.

Negative changes in MADRS total score indicate improvement.

The sections below describe the primary and sensitivity analyses performed for each primary and supplementary estimand.

5.3.2. Analysis Methods

Descriptive statistics of the observed values and the change from baseline (DB) at each time point in the DB phase, and FU phase (for participants who enter FU phase directly from DB phase) will be presented for MADRS total score by intervention group, along with a plot to display the change from baseline (DB) over time by intervention group.

5.4. Secondary Endpoint(s) Analysis

The analysis of key and other secondary endpoints will be conducted on the FAS (DB), unless otherwise specified.

5.4.1. Key Secondary Endpoint 1

The key secondary efficacy endpoint 1 is the change from baseline (DB) in CCI total score at Day 43 in participants for FAS (DB).

5.4.1.1. CCI (CCI

5.4.1.1.1. Definition

The CCI (CCI CCI

Imputation of total score is presented in Section 5.1.3.

Positive changes in CCI total score indicate improvement.

5.4.1.1.2. Analysis Methods

Descriptive statistics for the change in CCI total score over time will be presented for the DB treatment phase by intervention group. A line plot will be provided for the change from DB baseline overtime by intervention group.

Additionally, descriptive statistics of observed values and change from baseline (DB) over time in the subscales of the CCI CCI in the DB and FU (for participants who enter FU phase directly from DB phase) phases will be provided by intervention group for FAS (DB).

5.4.2. Key Secondary Endpoint 2

5.4.2.1.1. Definition

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. The CSFQ-14 recall period used in this study is the "past two weeks." 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. Normal SF is defined as a CSFQ 14 total score at DB Baseline of >41 for female and >47 for male participants.

Imputation of total score is presented in Section 5.1.3.

Positive changes in CSFQ-14 total score indicate improvement.

5.4.2.1.2. Analysis Methods

Descriptive statistics of the observed values and the change from DB baseline to each time point in the DB and FU phases (for participants who enter FU phase directly from DB phase) will be presented for the CSFQ-14 total score by intervention group for FAS_SF (DB). A line plot will be provided for the change from DB baseline overtime by intervention group. In addition, the summary statistics and the line plot will be presented separately for female and male participants.

No analyses will be performed for the Open-Label and the associated Follow-up phases for efficacy data.

5.5 Safety Analyses

All safety analyses will be based on safety (DB) or safety (OL) analysis sets based on randomized intervention in the DB phase, or treatment sequence in the OL phase, unless otherwise specified.

Safety analysis will be conducted separately for the DB and OL phases.

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.

5.5.1 Extent of Exposure

5.5.1.1 Definition

Study intervention duration in the DB phase is defined as (date of last dose of study intervention in the DB phase– date of first dose of study intervention) +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 DB phase.

Current antidepressant duration in the DB phase is defined as (minimum of end of study intervention and end of antidepressant use in the DB phase – maximum of start of study intervention and start of antidepressant use in the DB phase) +1.

Study intervention duration in the OL phase is defined as (date of last dose of study intervention in the OL phase – date of first dose of study intervention in the OL 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 OL phase.

Current antidepressant duration in the OL phase is defined as (minimum of end of aticaprant use and end of any antidepressants use in the OL phase – maximum of start of aticaprant use and start of any antidepressants use in the OL phase) +1.

5.5.1.2 Analysis

The following analysis of exposure will be performed:

For the DB phase:

- The number and percentage of participants who receive study intervention will be summarized by study intervention on Safety (DB) set.
- Descriptive statistics for duration of study intervention and of the current antidepressant (N, mean, SD, median, and range (minimum, maximum)) will be summarized by study intervention on Safety (DB) set.
- Duration of study intervention will be summarized by study intervention on Safety (DB) set in 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 phase:

- The number and percentage of participants who receive study intervention will be summarized by study intervention in the DB phase, and overall for the Safety (OL) analysis set.
- Descriptive statistics for duration of study intervention and of the current antidepressant (N, mean, SD, median, and range (minimum, maximum)) will be summarized by study intervention in the DB phase, and overall for the Safety (OL) analysis set.
- Duration of study intervention will be summarized by study intervention in the DB phase and overall for the Safety (OL) set in the following categories: 0-4 weeks, >4-8 weeks, >8-12 weeks, >12-16 weeks, >16-20 weeks, >20-24 weeks, >24 weeks.

5.5.1.3 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 will be summarized descriptively for each study intervention separately for DB and OL phase.

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.

The summaries will be provided for Safety (DB) and Safety (OL) analysis sets for the respective phases.

5.5.2 Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the end of DB phase, or through the end of DB or OL phase if the participants continue to OL treatment phase, is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention (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 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:

- **Double-blind treatment phase:**
    - For participants who continue into the OL phase: AEs during the DB phase will satisfy the condition: DB phase start date ≤ AE onset date < Date of last dose of study intervention in the DB phase.
    - For participants who do not continue into the OL phase: AEs during the DB phase will satisfy the condition: DB phase start date ≤ AE onset date ≤ Date of last dose of study intervention in the DB phase.
- **Open-Label-treatment phase:** AEs during the OL phase will satisfy the condition: OL phase start date ≤ AE onset date ≤ Date of last dose of study intervention in the OL phase.
- **Follow-up phase:** AEs that are assigned to the FU phase will not be considered as treatment-emergent. AEs during the FU phase will satisfy the condition: FU phase start date ≤ AE onset date ≤ FU phase end date.

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

- **Double-blind treatment phase:** AEs during the DB phase will satisfy the condition: DB phase start date ≤ AE onset date/time < OL phase start date/time.
- **Open-Label-treatment phase:** AEs during the OL phase will satisfy the condition: OL phase start date/time ≤ AE onset date/time ≤ Date of last dose of study intervention in the OL phase.

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

Summary tables will be provided for DB and OL phase separately:

- AEs (all AEs, all TEAEs, and TEAEs with incidence of at least 5% in any treatment group)
- Deaths
- Serious TEAEs (SAEs)
- AEs leading to discontinuation of study intervention
- AEs leading to treatment interruption
- AEs by severity
- AEs by relationship to study intervention
- AEs of special interest: Special interest of AE includes CCI [redacted] CCI [redacted] and CCI [redacted] CCI [redacted] CCI [redacted] For each AESI during the DB phase, 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. For each AESI during OL phase, the above summary will be provided if there is more than one event during OL phase.
- AEs of clinical interest
  - CCI [redacted]
  - 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 who:

- Died
- Had SAEs
- Had TEAEs leading to discontinuation of study intervention

- Had AEs of special interest
  - Special interest AEs include CCI [redacted] and CCI [redacted]
- Had AEs of clinical interest
  - CCI [redacted]
  - Suicide/Self-injury (First Sub SMQ)
  - AEs suggestive of abuse potential

AE during the follow-up phase will be presented in a listing.

5.5.3 Additional Safety Assessments

5.5.3.1 Clinical Laboratory Tests

Clinical laboratory test values collected in the DB and OL phases will be considered "treatment-emergent markedly abnormal" (TEMA) using the criteria relative to baseline (DB) defined by the sponsor listed in Appendix 7.

- If the post-baseline value is above the upper limit of the markedly abnormal criteria and the baseline (DB) value is below the upper limit, then the post-baseline marked abnormality will be considered TE. The same applies to the post-baseline 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 (DB) value is missing, a post-baseline 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 DB phase using Safety (DB) analysis set, and for the OL phase using the Safety (OL) analysis set.

- Descriptive statistics and the change from baseline will be summarized at all scheduled time points in the DB phase/OL phase by study intervention group. Note that for the DB phase, the baseline (DB) will be used and for the OL phase, the baseline (OL) is used.
- The number and percentage of participants with treatment-emergent markedly abnormal values during DB phase /OL phase relative to baseline (DB) will be presented by study intervention group or treatment sequence 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 DB phase /OL phase. Additionally, 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 respectively for DB phase and for OL phase. Participants with baseline (DB) 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 (DB) will be provided for the DB and OL phases. A listing of participants with ALT $\geq$ 3* ULN or AST values $\geq$ 3*ULN) and participants with hepatic toxicity (suspected Hy's Law cases) relative to baseline (DB) in the DB and OL phase will be provided.

5.5.3.2 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.

Abnormality criteria (based on criteria defined table 4 below) will be applied to post-baseline values in the DB and OL phases. Post-baseline values will be considered treatment-emergent if they meet both value and change criteria. Note that for the post-baseline values in the DB and OL phases, the abnormality criteria are relative to baseline (DB).

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

- Treatment-emergent will be concluded if the post-baseline value is above the upper limit and the baseline 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 value is missing, a post-baseline 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^{o}C
	Abnormally low	<35.5^{o}C
Weight	Abnormally high	increase ≥7% from baseline
	Abnormally low	decrease ≥7% from baseline

The following analyses will be performed:

- Change from the baseline (DB) will be summarized over time in the DB and FU (for participants who enter FU phase directly from DB phase) phases for the Safety (DB) analysis set. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

- Change from the baseline (OL) will be summarized over time in the OL and FU (for participants who enter FU phase directly from OL phase) phases for the Safety (OL) analysis set. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.
- Incidence of treatment-emergent clinically important vital signs relative to baseline (DB), as defined in Table 3, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign respectively for the DB phase for the Safety (DB) analysis set, and for the OL phase on Safety (OL) phase.
- A listing of participants with treatment-emergent clinically important abnormalities relative to baseline (DB) in vital signs during the DB, OL and FU phases will be presented for the Safety (DB) analysis set, along with a listing of clinical important vital sign measurements.

5.5.3.3 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 ECG 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	≤30
	Concern	>30 – 60
	Clear concern	> 60
QTc value	Normal	≤450 for male, ≤470 for female
	> 450 – 480 for male, > 470 – 480 for female	>450 to ≤480 for male, >470 to ≤480 for female
	> 480 – 500	>480 – ≤500
	> 500	> 500

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

Post-baseline abnormalities will be compared with the baseline (DB) result:

- Treatment-emergent will be concluded if the post-baseline value is above the upper limit and the baseline 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 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 respectively for the DB phase using Safety (DB) analysis set, and for the OL phase using Safety (OL) analysis set.
- The number and percentage of participants with QTc interval increases from baseline (DB) to the maximum postbaseline value and each post dose time point will be summarized respectively for the DB phase using Safety (DB) analysis set, and for the OL phases using Safety (OL) analysis set.
- Shift table will be provided from baseline (DB) to maximum post baseline QTc interval respectively for DB phase using Safety (DB) analysis set, and for the OL phase using Safety (OL) analysis set.

- Descriptive statistics of ECG parameters and change from baseline (DB) will be summarized at each scheduled time point for DB phase for the Safety (DB) analysis set.
- Descriptive statistics of ECG parameters and change from baseline (OL) will be summarized at each scheduled time point for the OL phase using Safety (OL) analysis set.
- The interpretation of the ECGs as determined by a central reader will be displayed by the number and percentage of participants meeting the normality criteria. The interpretation will be summarized over time respectively for the DB phase using Safety (DB) analysis set, and for the OL phase using Safety (OL) analysis set.
- The number and percentage of participants with treatment-emergent ECG values outside predefined limits relative to baseline (DB) will be presented by study intervention over time respectively for the DB phase using Safety (DB) analysis set, and for the OL phase using Safety (OL) analysis set.

Listings of ECG abnormalities (see Table 5) and abnormal QTc values in the DB and OL phases will also be provided SAF (DB) analysis set.

5.5.3.4 Other Safety Parameters

5.5.3.4.1 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 (DB) to the maximum post-baseline score pertaining to suicidal ideation or suicidal behavior (i.e., scores 1 to 10) will be summarized by study intervention for the DB phase using Safety (DB) analysis set, and by study intervention sequence for the OL phase using Safety (OL) analysis 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 (DB) to the maximum postbaseline category will be summarized by study intervention respectively for the DB phase using Safety (DB) analysis set, and for the OL phase using Safety (OL) analysis set.

A frequency distribution of the scores for the 11 categories (0 to 10) will be provided by study intervention at each time point respectively for the DB phase using Safety (DB) analysis set, for the OL phase using Safety (OL) analysis set. In addition, the number and proportion of participants with non-suicidal self-injurious behavior (a score of 11) will be provided by study intervention at each time point for each phase.

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.

5.6 Other Analyses

5.6.1 Pharmacokinetics

Bioanalysis of PK samples will be performed, and the concentration data will be included in a separate bioanalytical sample analysis report..

5.6.2 Biomarkers

No biomarker analyses will be performed for this study.

5.6.3 Definition of Subgroups

No subgroup analyses are planned for the final analysis for the abbreviated CSR.

5.7 Interim Analyses

5.7.1 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
C-SSRS	Columbia suicide severity rating scale
CSFQ-14	Changes in Sexual Function Questionnaire
CI	Confidence interval
CRF	Case report form
CCI	CCI
DB	Double-blind
DPS	Data Presentation Specifications
ECG	Electrocardiogram
EU	European union
FAS (DB)	Full analysis set (DB)
FAS SF (DB)	Full analysis Set-Sexual Functioning
FAS (OL)	Full analysis set (OL)
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
MAR	Missing at random
MDD	Major depressive disorder
MDD ANH+	MDD with moderate-to-severe anhedonia
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
NSAIDs	Non-steroidal anti-inflammatory drugs
OL	Open-Label
PK	Pharmacokinetic(s)
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SHAPS	Snaith-Hamilton Pleasure Scale
SMQ	Standardized MedDRA Query
SNRI	Selective norepinephrine reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitor
TE	Treatment emergent
WHO-DD	World health organization drug dictionary

6.2. Appendix 2 Changes to Protocol-Planned Analyses

As the study 67953964MDD3007 is prematurely terminated, the final analyses will be conducted descriptively, focusing on the full safety data and partial efficacy data limited to the primary and the key secondary endpoints. No hypothesis testing will be performed. No analyses for other secondary or exploratory endpoints will be conducted.

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 DB baseline that will be summarized by intervention group and overall for the FAS(DB) and FAS_SF(DB) analysis sets. The demographic variables at DB baseline and OL baseline will also be summarized by intervention group sequence and overall for the Safety (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 maximum]).
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: 18-34, 35-54, 55-64	
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)	
Tabacco use (Yes, No)	
Cannabis use (Yes, No) and Frequency of Cannabinoid use	
BMI (underweight <18.5 kg/m^2, normal 18.5-<25 kg/m^2, overweight 25-<30 kg/m^2, obese >=30 kg/m^2, morbidly obese>=40 kg/m^2)	
Employment status (any type of employement, any type of unemployment, other) [b]	

[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.

The baseline disease characteristics listed in Table 7 below will be summarized for their values at DB baseline by intervention group and overall for the FAS(DB) FAS_SF(DB), and Safety(OL) analysis sets. In addition, the baseline disease characteristics at OL baseline will be presented for Safety (OL) set.

Table 7: Psychiatric History at DB 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 SHAPS total score	
Baseline CSFQ-14 total score (applicable for FAS_SF (DB) analysis set only)	
Baseline CSFQ-14 total score - Female (applicable for FAS_SF (DB) analysis set only)	
Baseline CSFQ-14 total score -Male (applicable for FAS_SF (DB) analysis set only)	
Baseline CCI total score	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
Current antidepressant type (SSRI/SNRI)	
Presence of CCI Medical History (Yes, No)	
Screening C-SSRS category (no event, suicidal ideation, suicidal behavior)	

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 FAS and safety analysis sets.

- 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 DB and OL phases for safety (DB) and safety (OL) analysis sets, respectively. 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, prior medications other than antidepressants, and prior medications of special interest will be summarized by ATC level 2 and level 4 terms and base preferred term.

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
CCI [redacted]
CCI [redacted]
Medications for treatment of CCI [redacted]
Medications for treatment of CCI [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.

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 this study. QTL parameters will be summarized. More details are described in the Critical Data Oversight Plan (CDOP).

7. REFERENCES

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