Janssen Research & Development

Statistical Analysis Plan

A Randomized, Double-blind, Multicenter, Parallel-Group, 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

Protocol 67953964MDD3002; Phase 3

JNJ-67953964 (aticaprant)

Amendment 3

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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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VERSION HISTORY

Table – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
6.0	04Oct 2024	Removed Appendix 14 and Appendix 15 Statistical Analysis Plan for Japan/China-specific protocol	Details about the analysis sets and statistical analyses for these countries/territories will be described in separate analysis plans specific to Japan (if needed) and China.
5.0	09Aug 2024	Minor typo fix	
4.0	08Aug 2024	Section 5.4.1.1.4 Mediation analysis: updated the direction of the arrow in the mediation analysis figure	To clarify
		Section 6.1 Appendix 1 List of Abbreviations: updated the contents for MDD_WOANH_MS and MDD_WOANH_MS	To be consistent with analysis set definition
		Section 6.3: removed "MDD Anhedonia status" from the psychiatric history table	The information will be presented in the table of summary of analysis sets
		Section 6.14, 6.15: Replaced FAS_ANH- with newly defined non-enriched populations	Replaced the FAS_ANH- analysis set with the newly defined non-enriched populations for the statistical analysis plan for the Japan and China
		Section 7: deleted citations that are not referenced in the main body of the document	For consistency
3.0	31Jul 2024	Sections 1 , 1.1, 1.2, 3, 5.1.4: replaced MDD ANH- with Non-PAP	Non-PAP more accurately reflects the population, i.e., subjects who are not in the primary analysis set.
		Section 4, 5.1, 5.6.1, 5.6.1.1, 6.3: Replaced FAS_ANH- with newly defined non-enriched populations	The FAS_ANH- population will not be analyzed as a separate group as a portion of this population includes participants with prominent anhedonia CCI [redacted] Hence, replaced the analysis set with the newly defined non-enriched populations.
		Sections 5.1.4, 5.4.2.3.2: Removed MDD ANH-	Same as above
		Section 5.1.4 Pooling Algorithm: Further details added for clarity	To clarify
		Section 5.3.2.1.1 Primary Analysis: Algorithms for MMRM with unstructured and structured covariance implemented based on the FDA's instruction.	Based on FDA comments
		Sections 5.3.2.1.3, 5.4.1.1.4: Added additional analyses for the newly defined non-enriched populations. Removed interaction test for the All MDD group. Deleted analysis of additional sub-populations	The All MDD group contains non_PAP, the group of participants that does not reflect the non-enriched population of interest. Formal statistical analyses will not be performed due to insufficient sample size in non-enriched subgroups.

SAP Version	Approval Date	Change	Rationale
		Section 5.4.1.1.4 baseline MADRS added in ANCOVA mediation analysis for the change in DARS total score.	To help address the potential mediator-outcome confounding.
		Section 5.6.2: Added additional AE summaries	To better characterize the safety profile of aticaprant
		Section 5.6.3.1 Laboratory Tests: further detail added for hepatic abnormality. Deleted shift table.	To clarify. Shift table is not needed for interpretation of safety profile as aticaprant use is not associated with metabolic effects and there are no metabolic related endpoints.
		Section 5.6.3.4.2 ASEX: Subgroup of responder status by MADRS at Day 43 removed	It is more appropriate to explore the subgroups at baseline.
		Section 5.7.3: New subgroups added	To better characterize the treatment effect in various sub-groups
		Section 6.3, Table 7 demographic variables and Table 8 psychiatric history: demographic and baseline variables added	To better characterize the study population
		Throughout the document: Added additional information for clarity	To clarify
2.0	26 Feb 2024	Updated “Subjects” to “participants” throughout the document	To be consistent with the template
		Replaced “actual value” with “observed value” throughout the document	To use a more accurate term
		Section 1.1 Objectives and Endpoints: minor updates to descriptions for endpoints	Updated to align with protocol amendment 1.
		Section 3 Updated the sample size determination section	To be consistent with the modification to the criteria that define MDD ANH+.
		Section 5 General Considerations: Updated the stratification criteria based on MDD ANH status in the interactive web response system (IWRS).	To clarify the new stratification criteria for MDD AHN status
		Section 5.1.1 Added “Start and end dates for the follow-up phase are only defined for participants who continue into the follow-up phase.”	To clarify
		Table 1 Merged scales with the same assessment schedules together	To simplify the table
		Section 5.3.2 Updates made to primary estimand -ROW	To clarify population and intercurrent events
		Section 5.3.2.1 Updated delta adjustment analysis and added an additional sensitivity analysis for MMRM with an additional fixed effect factor of MDD ANH status (MDDANH1, MDDANH2).	To clarify delta adjustment and provide further sensitivity analysis
		Section 5.3.2.1.3 Other analysis: removed forest plot for LS mean change of MARDS for FAS_ANH+, FAS_ANH- and FAS_All. Updated the sub-population planed for FAS_All, CCI [redacted] and added sub-population based on MADRS item 8	To simplify analyses planed. To Update SHAPS cut off and address FDA request

SAP Version	Approval Date	Change	Rationale
		Section 5.3.2.1.3 Removed mediation analysis of change of MADRS mediated by change of DARS	To clarify the interest of the mediation analysis is the evaluation of the effect of aticaprant on anhedonia that is independent from the effect on depression.
		Section 5.5.1.2, 5.5.1.5 and 5.5.1.6 Updated descriptions of SHAPS, PGI-C, and GAD-7	To clarify
		Section 5.5.1.8 Updated analysis part of EQ-5-D	To clarify
		Section 5.6.1 Extent of Exposure Updated the definition of total number of dosing days Section 5.6.1.1 Updated the calculation of compliance for current AD	To clarify
		Added "DB phase" for safety analysis in Section 5.6.2 and 5.6.3	To clarify the analysis will only be performed in DB phase
		Section 5.6.2 Added additional analyses for AESI	To clarify the details of analyses for AESI
		Added "RR interval" to Table 6	To clarify the additional parameter included
		Section 5.6.3.4.1 Added a listing for C-SSRS	To clarify additional analysis
		Section 5.6.4.3.2 Added subgroup analyses for ASEX	To provide additional analysis
		Removed Analysis for "menstrual Cycle Tracking"	Excluded analysis with limited value in a short term study
		Section 5.7.3 Updated the definition of subgroup "Race", merged categories with few subjects	To clarify the subgroups that will be explored
		Updated Appendix 9	To clarify when COVID-19 related analysis will be performed
		Appendix 14 and 15 Updates made to the population of primary estimand -Japan and China	To clarify and be consistent with primary estimand - ROW
		Other minor changes in wording/terminology made throughout the document.	To clarify
1	20 Mar 2023	Not Applicable	Initial release

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for study 67953964MDD3002.

The 'MDD ANH-' population that is referenced in the protocol has been renamed in the SAP as non-primary analysis population or 'non-PAP' to more accurately reflect the population, as some subjects in this population had prominent anhedonia CCI [redacted]

1.1. Objectives and Endpoints

This is a randomized, double-blind, multicenter, parallel-group, 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.

OBJECTIVES AND ENDPOINTS

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 improving anhedonia in adult participants with MDD ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI	• Change from baseline to Day 43 in Dimensional Anhedonia Rating Scale (DARS) total score
Other Secondary	
To evaluate the efficacy of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant in adult participants with MDD ANH+ who have had an inadequate response to the current antidepressant therapy (SSRI or SNRI) on the following:	
• Depressive symptoms (clinician-reported)	• Change from baseline over time in MADRS total score.
• Response of depressive symptoms (clinician-reported)	• Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score from baseline to Day 43.
• Remission of depressive symptoms (clinician-reported)	• Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤10 at Day 43.

Objectives	Endpoints
• Symptoms of depression (patient-reported)	• Change from baseline to Day 43 in Patient Health Questionnaire, 9-Item (PHQ-9) total score.
• Anhedonia symptoms (patient-reported)	• Change from baseline over time in DARS total score. • Change from baseline over time in the PHQ-9 anhedonia-specific item (PHQ-9, item 1). • Proportion of participants with a score less than 2 in the PHQ-9 anhedonia-specific item (PHQ-9, item 1) at Day 43.
• Social functioning (patient-reported)	• Change from baseline over time in the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form v2.0 – Ability to Participate in Social Roles and Activities - 8a (PROMIS-APS 8a)
Safety	
All participants - Safety will be assessed for all MDD participants (adult and elderly).	
• To assess the safety and tolerability of aticaprant 10 mg as adjunctive therapy to an antidepressant (SSRI or SNRI) in all MDD participants (adult and elderly) in short-term treatment compared with placebo.	• AEs, including AEs of special interest (AESI) • Vital signs • 12-lead ECG • Laboratory parameters • Weight/Body Mass Index (BMI) • Suicidality assessment using the C-SSRS • Withdrawal symptoms assessment using the physician Withdrawal Checklist 20-items (PWC 20). • Proportion of participants with clinically relevant sexual dysfunction over time in the Arizona Sexual Experiences Scale (ASEX) score.
Exploratory	
To assess the efficacy of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant (SSRI or SNRI) in adult participants with MDD ANH+ (PAP), adult non-PAP , and all MDD participants (adult and elderly participants with MDD ANH+ and non-PAP) who have had an inadequate response to their current antidepressant therapy on the following:	
• Depressive symptoms (clinician and patient-reported).	• Change from baseline over time in the MADRS total score (applicable to adult non-PAP and All MDD). • Change from baseline over time in the MADRS-6 score.

Objectives	Endpoints
	• Change from baseline over time in PHQ-9 total score.
• Anhedonia symptoms (patient-reported)	• Change from baseline over time in DARS total score (applicable to adult non-PAP and All MDD). • Change from baseline over time in the subscales of the DARS (hobbies/pastimes, food/drink, social activities, and sensory experiences). • Change from baseline in the Snaith-Hamilton Pleasure Scale (SHAPS) over time. • DARS improvement response at Day 43 (increase in DARS total score ≥ meaningful change threshold [or range of thresholds] determined by anchor-based analyses of blinded interim data, as indicated in Section 5.8)
• Severity of depressive symptoms (clinician- and patient- reported)	• Change from baseline over time in the Clinical Global Impression-Severity (CGI-S) score • Change from baseline over time in the symptoms of depression as assessed using the Patient Global Impression of Severity (PGI-S) for depression.
• Severity of anhedonia symptoms (patient-reported)	• Change from baseline over time in anhedonia symptoms using the PGI-S for anhedonia. • Score at Day 43 in anhedonia symptoms using the PGI-C for anhedonia.
• Health-related quality of life (patient-reported)	• Change from baseline over time in health-related quality of life EQ visual analogue scale (EQ-VAS) and health status, as assessed by the European Quality of Life, 5 Dimension, 5Level (EQ-5D-5L) questionnaire. • Change from baseline over time in health-related quality of life as assessed by the Quality of Life in Depression Scale (QLDS).
• Anxiety symptoms (patient-reported)	• Change from baseline to Day 43 in symptoms of anxiety using the Generalized Anxiety Disorder 7-item Scale (GAD-7).

Objectives	Endpoints
Clinical Pharmacology Assessments	
• To assess the pharmacokinetics of aticaprant (10 mg) in participants with MDD when used as adjunctive treatment. • To assess the exposure-response relationship of aticaprant and MADRS in participants with MDD. • To assess the exposure-response relationship of aticaprant and selected adverse events.	
Biomarker Signatures	
• To confirm the diagnostic biomarker signature identified in Study 67953964MDD3001 which might be predictive of clinical improvement on depression symptoms and anhedonia upon treatment with aticaprant. • To explore genetic and other factors that may influence the efficacy, pharmacokinetics, safety, or tolerability of aticaprant.	
• To confirm the diagnostic value of biosignature identified in Study 67953964MDD3001 to predict treatment response.	• Change from baseline to Day 43 in MADRS total score in defined biosignature positive participants and respective biosignature negative participants.
Digital Biomarkers	
• To evaluate the association between digital biomarkers at baseline (derived from speech, video, and Reward Learning Task [RLT]) and treatment response. • To evaluate the correlation of digital biomarkers with measures of anhedonia and other depression characteristics, and Biomarker Signature defined subgroup. • To evaluate the change of exploratory digital endpoint (for example, RLT from block 1 to block 2 or from block 1 to block 3, learning rate, and reward sensitivity [ie, baseline to Day 43]).	

1.2. Study Design

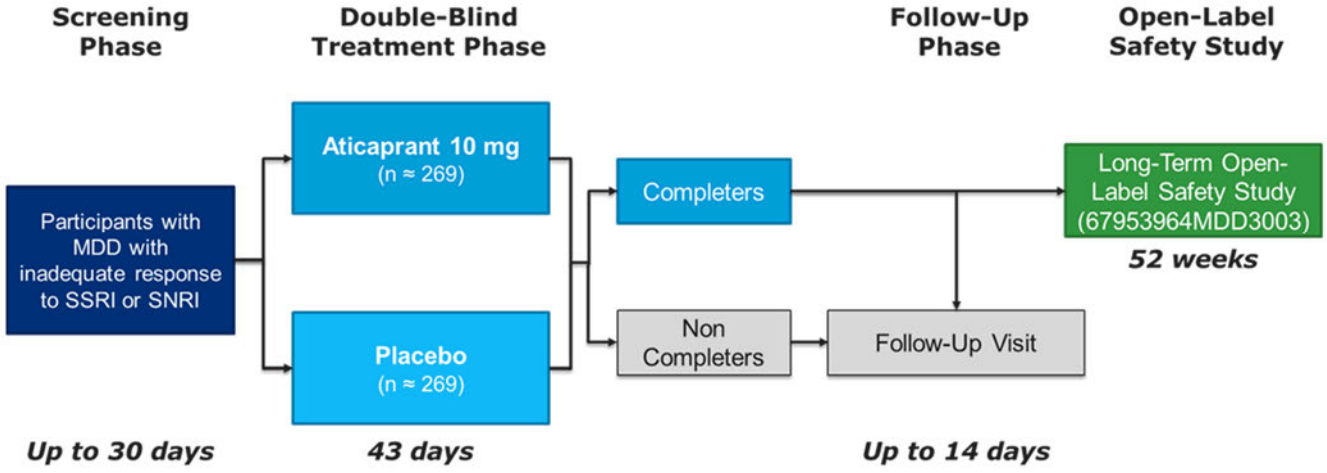
This is a multicenter, randomized, double-blind, parallel-group, placebo-controlled study to assess the efficacy, safety and tolerability of adjunctive aticaprant 10 mg in adult participants (18 to 64 years of age, inclusive) who have major depressive disorder (MDD) with moderate-to-severe anhedonia (MDD ANH+, also referred to as the Primary Analysis Population [PAP]), adult participants who do not qualify for MDD ANH+ (non-PAP), and elderly participants (65 to 74 years of age, inclusive) with MDD (ANH+ and non-PAP). All participants must have had an inadequate response to a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) in the current depressive episode.

In addition, PK, pharmacogenomics, and biomarkers will also be evaluated.

This study will consist of the following phases:

- Screening Phase (evaluate eligibility): up to 30 days prior to first dose administration.
- Double-blind (DB) Treatment Phase: 43 days.
- Follow-up Phase: up to 14 days.

Figure 1: Schematic Overview of the Study



Approximately 538 participants (430 adult and 108 elderly) will be randomized. The adult MDD ANH+ population randomized to aticaprant 10 mg or placebo will be included in the primary and key secondary analysis.

Additionally, approximately 118 participants from China and/or 54 participants from Japan (if participating) will be enrolled in the study.

All participants will continue to take their current SSRI or SNRI antidepressant therapy (at the same dose and at approximately the same time of the day) throughout the study.

Abbreviations: SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor.

Participants will be randomized in a 1:1 ratio to receive aticaprant at 10 mg or placebo for 42 days. The study intervention will be administered orally as 2 film-coated tablets to be taken together, once daily, around the same time and preferably in the morning.

The study population will include participants 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 65 years of age or older must have had the first onset of depression prior to 55 years of age. Eligible participants must have a 17-item Hamilton Depression Rating Scale (HDRS-17) total score ≥20 at the first and second screening interviews with no greater than 20% improvement from the first to the second independent HDRS-17 assessments at screening. Moreover, all participants must have had an inadequate response to at least 1 oral antidepressant treatment (SSRI or SNRI), administered at an adequate dose (therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current depressive episode. An inadequate response is defined as <50% reduction in depressive symptom severity but with some improvement (>0%; i.e., there may be minimal to moderate symptomatic improvement since the initiation of treatment, but some of the initial symptoms are still present, troubling to the participant and affecting behavior and function) as assessed by the MGH-ATRQ. The inadequate response must include the participant's current SSRI/SNRI treatment.

All participants will continue their current SSRI/SNRI antidepressant at the same dose without change and taken approximately around the same time of the day 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 have completed the Day 43 visit of the DB Treatment Phase, including the MADRS assessment at the end of the 6-week DB Treatment Phase (i.e., Day 43 MADRS), and have not discontinued study intervention early during the DB Treatment Phase.

Participants who have completed the DB Treatment Phase (Day 43) and were compliant to the study intervention may be eligible to participate in a separate 52-week open-label long-term safety study 67953964MDD3003. The investigator and the participant will determine, based on efficacy and tolerability of the DB treatment, whether it is in the best interest of the participant to continue treatment in the open-label long-term safety study. The decision to enroll in the 67953964MDD3003 study or enter the Follow-up Phase will be documented in the electronic case report form (eCRF). Participants who complete the DB Treatment Phase, are eligible and decide to roll-over to the open-label long-term safety study are not expected to complete the Follow-up Phase.

Participants who complete the DB Treatment Phase will be considered to have completed the study if they roll over to Study 67953964MDD3003 or complete the Follow-up Visit, including the MADRS, DARS, and PWC-20 assessments at this visit. If a participant enters the open-label safety study, the Follow-up Visit will not be conducted.

Participants who discontinue study intervention in the DB Treatment Phase will be considered to have completed the study if they completed the Follow-up Phase, including the MADRS, DARS, and PWC-20 assessments at this visit.

Participants who discontinue study intervention early (i.e., prior to completion of Day 43 visit) or who are non-compliant to the study intervention (i.e., have missed either 4 or more consecutive doses of study intervention or a total of 8 or more doses during the DB Treatment Phase) will not be eligible to participate in the open-label safety study.

Participants who discontinue study intervention during the DB Treatment Phase and participants who completed of the DB Treatment Phase who are not rolling-over to the open-label long-term safety study (67953964MDD3003) will complete the End-of-Treatment (EOT)/Early Withdrawal (EW) visit and will then enter the Follow-up Phase of the study.

No study intervention will be administered during the Follow up Phase; further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or participant's treating physician, and changes to current antidepressant treatment are permitted in this study phase.

The worldwide COVID-19 pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or study participants become potentially exposed to or infected with COVID-19. To assure the safety of study participants, maintain compliance with Good Clinical Practice (GCP), and minimize risks to study integrity, if necessary, in consultation with the sponsor, the method of assessments may be changed (e.g., paper assessments replaced by electronic assessments and vice versa). In addition, site visits may be replaced with telephone, internet-based video-conferencing applications, or home visits by qualified healthcare professionals (HCP). Rating scales/safety assessments can continue to be administered via video teleconferencing (MADRS) or phone (other assessments). Every effort should be made to complete the MADRS assessment via video teleconferencing and within the scheduled timeframe; if this cannot occur, the sponsor medical monitor or delegate should be contacted for direction. Normal procedures, as detailed in this protocol, will be resumed as soon as possible thereafter. For participants who receive an approved or authorized vaccine, it is recommended that this occurs at least 5 days prior to the start of dosing, or once randomized at least 5 days prior to the next scheduled visit.

An Independent Data Monitoring Committee (IDMC) will be commissioned to periodically review safety data for this study.

2. STATISTICAL HYPOTHESES

This study is designed to show that the treatment effect in improving depressive symptoms (as measured by change from baseline on Day 43 in MADRS total score) of aticaprant 10 mg as an adjunctive MDD treatment is superior to placebo in adult participants with MDD ANH+.

If μ_T is the mean change in MADRS total score for the aticaprant 10 mg group and μ_P is the mean change in MADRS total score for the placebo group, then the hypothesis can be written as follows:

H_0: $\mu_T - \mu_P \geq 0$ vs

H_1: $\mu_T - \mu_P < 0$

Superiority can be concluded if the two-sided p-value for the testing of the hypothesis above is less than 0.05 (2-sided) and the direction is consistent with the alternative hypothesis.

3. SAMPLE SIZE DETERMINATION

Approximately 538 participants, including adult (18 to 64 years of age, inclusive) and elderly (65 to 74 years of age, inclusive) will be randomized in this study.

Participants entering the DB Treatment phase will be randomized in a 1:1 ratio to adjunctive placebo, and adjunctive aticaprant 10 mg. A minimum of 324 adult participants with MDD ANH+ and approximately 106 adult non-PAP will be randomized.

Assuming an effect size of 0.38 for the change in MADRS total score, and a 1-sided significance level of 0.025 (equivalently, 2-sided 0.05), this sample size of 324 adult participants with MDD ANH+ will provide approximately 88% power for the comparison between adjunctive aticaprant 10 mg and adjunctive placebo for the primary efficacy endpoint (in adult participants with MDD ANH+), accounting for a dropout rate of approximately 15%.

The effect size used in the sample size calculation was based on the results of Study 67953964MDD2001 where the effect size was 0.39 (mean difference between treatment groups of -3.4 and a pooled standard deviation of 8.72) for the change from baseline to Day 43 in MADRS total score for the relevant study population, and clinical judgment.

It is expected that approximately 108 elderly participants (65 to 74 years of age, inclusive) will be randomized in the study. This subset of participants will be analyzed as an exploratory evaluation and will not be included in the primary analysis set.

Additionally, approximately 118 participants from China will participate in the study. In the event Japan participates in the study, approximately 54 participants will be enrolled in this country/territory. The details are described in the respective country/territory-specific amendments to the protocol.

Note: The sample size assumptions are based on the criteria that define MDD ANH+. These criteria have been modified from the protocol, which are documented in the protocol addendum. Based on the results from the Phase 2 study using the new criteria, the study is powered for the original planned number of 324 participants with MDD ANH+. The table below provides the differences between the protocol and the SAP.

	Phase 3 study		**Results from Study 67953964MDD2001**		
Document	**Assumed Effect Size**	**Power**	**Effect size**	**Mean treatment difference**	**Pooled standard deviation**
Protocol	0.4	90%	0.45	-4.1	8.98
SAP	0.38	88%	0.39	-3.4	8.72

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The following analysis sets are defined for the participants enrolled in rest of world (ROW i.e., countries/territories other than China and Japan).

Population	Description
All Participants	All participants in ROW who sign the informed consent form (ICF)
Randomized	All participants in ROW who were randomized in the study
Full Analysis Set (ANH+) (FAS_ANH+)	All adult randomized participants in ROW with MDD ANH+ who take at least 1 dose of study intervention. This is the primary analysis population for the primary and key secondary efficacy endpoints.
MDD_WOANH_S Analysis Set	Adult randomized participants in ROW with CCI [redacted] who take at least 1 dose of study intervention.
MDD_WOANH_MS Analysis Set	Adult randomized participants in ROW with CCI [redacted] who take at least 1 dose of study intervention.
Full Analysis Set (All) (FAS_All)	All randomized participants (adult and elderly) in ROW with MDD ANH+ or non-PAP who take at least 1 dose of study intervention
Safety Analysis Set	All randomized participants (adults and elderly) in ROW who take at least 1 dose of study intervention.
Follow-up Analysis Set	All randomized participants in ROW who entered the follow-up phase after the double-blind treatment phase
Note: In order to assess the treatment effect in participants without anhedonia, analyses will be conducted for the MDD_WOANH_S and MDD_WOANH_MS analysis sets as noted in the relevant sections below.	

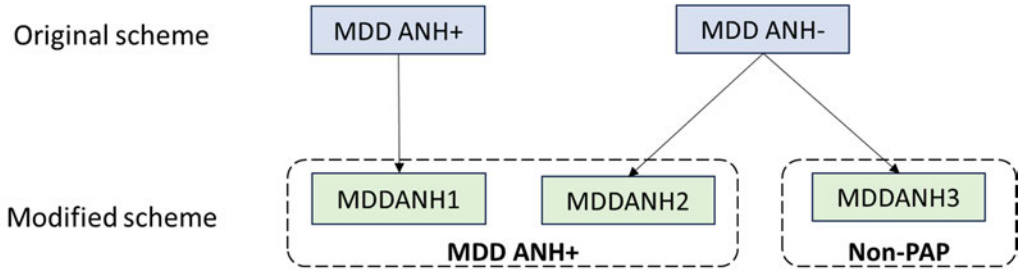
Due to Good Clinical Practice (GCP) issues, participants enrolled in the Scarpino site will be included in the randomized analysis set, but not in the efficacy and safety analysis sets. Patient profiles will be provided for these participants.

5. STATISTICAL ANALYSES

5.1. General Considerations

As indicated in Section 3 the criteria defining MDD ANH+ were modified while the study was ongoing. Hence the stratification criteria based on MDD ANH status was also modified in the interactive web response system (IWRS). While the original stratification consisted of two strata – MDD ANH+ and MDD ANH-, the modified stratification scheme consists of three strata – MDDANH1 CCI [redacted] MDDANH2 CCI [redacted] and MDDANH3 CCI [redacted] Details about the modification to the criteria are presented in the addendum to the protocol which is blinded to the study sites. The mapping of the different strata from the 2 schemes is presented in Figure 2.

Figure 2: MDD ANH Stratification in IWRS – Mapping of MDD ANH Strata between Original and Modified



For participants who were randomized under the original scheme, participants from the MDD ANH+ stratum will be classified under MDDANH1, and those from the stratum called MDD ANH- stratum will be classified into MDDANH2 and MDDANH3. For all the analyses described in this document the primary population of interest, i.e., adult participants with MDD with moderate-to-severe anhedonia (referred to as 'MDD ANH+' in the protocol), will include adult participants belonging to MDDANH1 and MDDANH2. Participants in the MDDANH3 stratum will be termed as the non-PAP group.

It is possible that the enrollment in Japan (if participating) and/or China may take significantly longer than the ROW. Therefore, so as not to delay ROW submissions, data from Japan and China will only be combined with the global data for local registration in the respective countries/territories. Analyses of efficacy data from the ROW will be used for submissions outside of Japan and China. Details about the analysis sets and statistical analyses for these countries/territories will be described in a separate document specific to Japan (if needed) and China.

The assessment of the primary and secondary (key and other) endpoints will be conducted on the FAS_ANH+, which includes adult (not elderly) participants with MDD ANH+ who were randomized to aticaprant 10 mg or placebo and took at least 1 dose of study intervention. The exploratory endpoints will be analyzed in adult participants with MDD ANH+ (FAS_ANH+), and all MDD participants (FAS_All: adult and elderly participants with MDD ANH+ and non-PAP). As the non-PAP group also consists of participants with moderate-to-severe anhedonia CCI [redacted] exploratory endpoints described in the protocol will not be analyzed for this population. Similar classification will be applied to elderly participants who are included in FAS_All.

The primary efficacy endpoint is the change in MADRS total score from baseline to Day 43 in adult participants with MDD ANH+. The key secondary endpoint is the change in DARS total score from baseline to Day 43 in this group of study participants.

5.1.1. Analysis Phases

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. The analysis reference end date of the double-blind treatment phase (DB phase 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.

Follow-up Phase

Start and end dates for the follow-up phase are only defined for participants who continue into the follow-up phase. The analysis reference start date of the follow-up phase (follow-up phase start date) is the day after the reference end date for the double-blind treatment phase. The analysis reference end date of the follow-up phase (follow-up phase end date) is the maximum of the date of the last visit in the follow-up 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 Visit Number	Time Interval	Time Interval (Day)*	Target Time Point
MADRS, DARS, CGI-S, PGI-S anhedonia, PHQ-9, PGI-S depression, PROMIS SF 8a, EQ-5D-5L	DB	2.1	Baseline (DB)	<=1	1
		2.3	Day 15	2 to 22	15
		2.5	Day 29	23 to 36	29
		2.7	Day 43	37 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
	FU	3.1	Follow-up	End of DB + 1 to End of FU	7-14
QLDS, ASEX	DB	2.1	Baseline (DB)	<=1	1
		2.5	Day 29	2 to 36	29
		2.7	Day 43	37 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
SHAPS	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.3	Day 15	2 to 22	15
		2.5	Day 29	23 to 36	29
		2.7	Day 43	37 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
GAD-7	DB	2.1	Baseline (DB)	<=1	1
		2.7	Day 43	2 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
PGI-C anhedonia	DB	2.7	Day 43	1 to End of DB	43
		DB final visit	Endpoint (DB)	1 to End of DB	
PWC-20	DB	2.7	Day 43	1 to End of DB	43
		DB final visit	Endpoint (DB)	1 to End of DB	
	FU	3.1	Follow-up	End of DB + 1 to	7-14
Vital Signs	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.3	Day 15	2 to 22	15
		2.5	Day 29	23 to 36	29
		2.7	Day 43	37 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
	FU	3.1	Follow-up	End of DB + 1 to End of FU	7-14
ECG	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB) Day 1: Postdose	<=1/ predose 1	1
		2.5	Day 29: Predose Day 29: Postdose	2 to 36	29
		2.7	Day 43	37 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
Hematology, Chemistry Urinalysis	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.7	Day 43	2 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
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 32	29
		2.6	Day 36	33 to 39	36

		2.7	Day 43	40 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
	FU	3.1	Follow-up	End of DB + 1 to	7-14
Weight/BMI	SCR	1.1	Screening	<1	
	DB	2.1	Baseline (DB)	<=1	1
		2.7	Day 43	2 to End of DB	43
		DB final visit	Endpoint (DB)	2 to End of DB	
	FU	3.1	Follow-up	End of DB + 1 to End of FU	7-14

*Relative to the first day of the DB 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.

Baseline (DB) is the last observation prior to or on the start date of DB phase. Endpoint (DB) is the last observation in the DB phase.

5.1.3. Imputation of Efficacy

Imputation for missing data in the primary and key secondary endpoint (MADRS and DARS) will include the following methods (Table 2).

Table 2: Imputation of Missing Efficacy Data

Imputation	Method/Rule
Multiple Imputation (MI) method	Delta Adjustment
Non-Responder	Participants with missing values will be imputed as non-responders for analyses that use imputed data.
Non-Remitter	Participants with missing values will be imputed as non-remitters for analyses that use imputed data.

Imputation of total scores will be performed for the efficacy scales as shown in Table 3 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 3: 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)
QLDS	34	6	Sum of non-missing item scores * (34 / number of non-missing items)

5.1.4. Country/Territory Pooling Algorithm

Pooling will be conducted if a sufficient number of participants are not randomized to a country/territory. If necessary, the countries/territories with fewer than 4 randomized participants will be combined for the purpose of analysis within each region (North America, Europe, South America, Asia, and Other). These countries/territories will be ordered according to the total number of participants. The pooling will be carried out sequentially beginning with the smallest countries/territories until the number of participants in the pooled analysis countries/territories is 4 or more. The size of any pooled analysis countries/territories should be as large as possible and not be larger than the size of the largest country/territory in the region. If the number of small countries/territories is large, and one pooled analysis country/territory cannot include all small countries/territories, then the second (or more) pooled analysis country/territory will be formed after the first one is filled with as many small countries/territories as possible. Pooled countries/territories as described are called analysis countries/territories and will be used in the analyses as country/territory effect.

Pooling will be conducted in adult participants with MDD ANH+. The same procedure will be applied for all MDD participants (adult and elderly participants with MDD ANH+ and non-PAP).

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 study by intervention group and overall for the all randomized, FAS_All and FAS_ANH+:

- Participants randomized
- Participants who received study intervention
- Participants who completed, discontinued and reasons for discontinuation of study intervention during double-blind phase
- Participants who completed, terminated and reasons for discontinuation of study
- Intercurrent events in the double-blind phase

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

Listings of participants will be provided for the following categories:

- Participants who discontinued double-blind study intervention
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention.

If deemed necessary, additional analyses of disposition data for assessing and mitigating the impact of COVID-19 on study outcome will be conducted as presented in Appendix 9**.**

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_ANH+.

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. Primary Estimand - ROW

This estimand is defined to address the primary objective when the study intervention is taken as directed.

Primary Trial Objective: 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 ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI.

Estimand Scientific Question of Interest: What is the antidepressant benefit from aticaprant 10 mg versus placebo as adjunctive treatment to a SSRI or SNRI in adult participants with MDD ANH+, who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI based on the change from baseline in MADRS total score if the participants take study intervention as directed?

This estimand is defined by the following 5 components:

Study Intervention:

- Experimental: Aticaprant 10 mg as an adjunctive treatment to SSRI or SNRI
- Control: Placebo as an adjunctive treatment to SSRI or SNRI

Population: Adult patients (18 to 64 years of age, inclusive) in ROW with a diagnosis of MDD ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI.

Variable: Change in MADRS total score from baseline to Day 43

Summary Measure: Difference in intervention means

Intercurrent events and their corresponding strategies:

Intercurrent Events	Name of Strategy for Addressing Intercurrent Events and Its Description
1. Discontinuation of study intervention only	Hypothetical strategy: as if the intercurrent event had not occurred
2. Discontinuation of both study intervention and current antidepressant	Hypothetical strategy: see above
3. Switch of study intervention only (ie, initiation of another antidepressant after discontinuation of study intervention)	Hypothetical strategy: see above
4. Switch of current antidepressant therapy only	Hypothetical strategy: see above
5. Switch of study intervention and current antidepressant therapy	Hypothetical strategy: see above

For participants experiencing multiple intercurrent events at the same time or switching study intervention and/or current antidepressant therapy after discontinuation of study intervention and/or current antidepressant therapy before/on the end of DB phase, intercurrent events in categories 3-5 will override the rest. For example, if a patient starts a new antidepressant medication the day after taking the last dose of their study intervention/current antidepressant therapy, this intercurrent event will be considered a switch of study intervention/current antidepressant therapy, and not a discontinuation. However, if more than one day passes between the last dose of their study intervention/current antidepressant therapy and the first dose of the new antidepressant medication, this situation will be considered a discontinuation of study intervention/current antidepressant therapy intercurrent event followed by a switch of antidepressant medication intercurrent event.

For all intercurrent events, data collected beyond 1 week from the occurrence of the event (or the first event in participants with multiple ICEs) including the data from the EOT/EW visit will be excluded from the analysis. No additional intercurrent events will be assigned beyond 1 week from the occurrence of the first intercurrent event.

Rationale for including data collected within 1 week from the occurrence of the intercurrent event: Given the weekly schedule of data collection (either via a telephone contact, or at a site visit) the expectation is that it could take up to a week for the participants to schedule the EOT/EW visit. This window of data collection post-ICE aligns with aticaprant's mean half-life ($t_{1/2}$) of 21.3 to 38.5 hours (IB Aticaprant 2022). Additionally, for the ICEs of switch to a new antidepressant treatment the time to an onset of initial effect for the most commonly prescribed antidepressants is typically at least 2 to 4 weeks (Khin, 2013; Yang, 2013).

5.3.2.1. Analysis Methods

5.3.2.1.1. Primary Analysis

The change from baseline in MADRS total score will be analyzed by a Mixed-Effect Model for Repeated Measures (MMRM) based on observed data. The fixed terms included in the model will be intervention group (aticaprant 10 mg and placebo), country/territory, time, and time-by intervention interaction, and the baseline score as a covariate. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. In case of convergence problems, with the default Newton Raphson algorithm, alternative approaches will be tried in the following order before using a structured variance-covariance matrix: Fisher scoring algorithm, and factor analysis structure. If the convergence issues persist with the unstructured variance-covariance matrix, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. A robust sandwich variance estimator will be used if a structured covariance matrix is implemented. Comparison between aticaprant 10 mg and placebo at Day 43 will be performed using the appropriate contrast. The least square (LS) mean (+/-SE) change from baseline and the difference of LS means (95% CI) will be presented over time.

Descriptive statistics of the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented for MADRS total score by intervention group.

Justification of MMRM using MAR assumption: The discontinuation rates observed in the Phase 2a Study 67953964MDD2001 were less than 5% in the 2 treatment arms (4.8% in aticaprant 10 mg, and 2.4% in placebo, see Appendix 12). There was no apparent pattern of trajectories of MADRS change from baseline among participants who completed the study compared with participants who discontinued study intervention within each intervention group. Additionally, there was no specific pattern of trajectories MADRS change from baseline for each dropout reason (Appendix 12). Based on these observations, it is considered reasonable to assume missing at random (MAR) as the missingness mechanism.

MAR assumption cannot be tested vs. MNAR using observed data, however, simulation findings (Siddiqui 2009) indicate that in the presence of a mixture of the 3 missing mechanisms (missing completely at random [MCAR], MAR, missing not at random [MNAR]) with differential dropout rates between treatment groups, the MMRM approach is able to re-estimate the true treatment difference consistently with a negligible bias and control Type I error rate. Therefore, the primary analysis for this estimand will be MMRM, with sensitivity analysis using the tipping point method to stress test the efficacy findings under MNAR assumption.

5.3.2.1.2. Sensitivity Analysis

Delta adjustment tipping point analysis

The sensitivity analysis for the primary Estimand – ROW will include the delta adjustment multiple imputation method which will be implemented on the MADRS total score if the results from the primary analysis show a significantly greater improvement in MADRS total score at Day 43 in aticaprant compared to placebo. This method will employ the following 3 steps:

Step 1 – Multiple Imputation (MI)

If there are participants with a non-monotone missing data pattern, datasets with only monotone missing data patterns will be created first by imputing the intermediate missing values using methods such as the MCMC (Markov Chain Monte Carlo) method. 500 imputations will be performed to create 500 unique datasets which now have monotone missing (ie., missing data one week after the participant experienced an intercurrent event) data pattern.

Analysis assumptions: Missing at random (MAR) is assumed for intermediate missing data (i.e., missing data between non-missing observations). Monotone missing data will first be imputed by MAR-based MI regression, and the imputed scores in the experimental intervention group will be adjusted to be worse than the other participants in same group with non-missing data as discussed below. Note: Data may be monotone missing due to participant discontinuation after the ICE, or may be deemed monotone missing per the hypothetical strategy as described in Section 5.3.2 where data collected beyond one week from the occurrence of the ICE will be excluded from the primary analysis.

The imputed values will be adjusted by adding δ_c to the imputed values for participants randomized to the control group and adding δ_A to the imputed values for participants randomized to the experimental intervention group. Delta-adjusted fully imputed datasets will be generated for different combinations of δ_c and δ_A values as defined below:

- $\delta_c = 0$ and $\delta_A = 0$ *to* Δ^* in increments of 1 (experimental group-only adjustment analysis)

  Adding positive values results in higher (worse) scores. Δ^* represents the adjustments leading to the 'tipping point', so the smallest delta adjustments values at which conclusions change from *favorable* (i.e. statistically significant: 2-sided p-value < 0.05 in favor of aticaprant) to *unfavorable* (fail to reject the null hypothesis of no intervention difference).

- Imputed values in both the experimental and the control groups will be adjusted using a range of delta values, and delta-adjusted fully imputed datasets will be generated for each combination.

These methods will be applied to all missing data under hypothetical strategy. In addition, another version of these methods will be implemented, where the delta adjustments will be applied to missing data hypothetical strategy except for those caused by discontinuation reasons due to COVID-19 (if deemed necessary), and for discontinuation reasons not related to study intervention including Lost to Follow-Up, Withdrawal by Subject or Other.

Step 2 – Analysis

Same MMRM analysis as described for the primary efficacy analysis will be performed for each set of the adjusted fully imputed datasets.

Step 3 – Pooling

Rubin's methodology will be applied to the MMRM results from the 500 imputed datasets to produce final inferences.

Between-group comparisons to placebo at Day 43 (e.g. 2-sided p-values, point estimates for intervention difference) will be displayed graphically for each considered δ_A, up to the 'tipping point' adjustment. For analysis of the imputed datasets using a range of delta-adjustments on both experimental and control groups, a tipping point two-way map will be generated.

The SAS code for the delta adjustment multiple imputation procedure is provided in Appendix 10.

Other sensitivity analysis

The change from baseline in MADRS total score for the primary population will be analyzed using the same MMRM model as for the primary analysis with an additional fixed effect factor for MDDANH status (MDDANH1, MDDANH2).

5.3.2.1.3. Other Analyses

Descriptive statistics of the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented for MADRS total score by intervention group for FAS_All. Change from baseline of MADRS total score will be analyzed for this analysis set using the same MMRM model as described for the primary endpoint in section along with the following additional terms in the model: ANH strata (MDDANH1, MDDANH2, MDDAH3) and age group (adult, elderly). LS mean changes from baseline (+/- SE) over time will be presented.

To assess the treatment effect in participants without anhedonia, descriptive statistics for the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented for MADRS total score by intervention group for the MDD_WOANH_S and MDD_WOANH_MS analysis sets.

To address an FDA request to provide a supplementary analysis using a more direct measure to define moderate-to-severe anhedonia, analysis for change from baseline of MADRS total score at Day 43 for adult participants in FAS_All will be performed in a similar manner as specified in section 5.3.2.1.1 for the sub-populations below:

- MADRS Item 8 score (≥2, <2)

The difference of LS mean change (95% CI) at Day 43 will be presented for each sub-population in a forest plot. Additionally, descriptive summaries of change over time in MADRS total score will be provided for the two sub-groups.

5.4. Secondary Endpoint(s) Analysis

The assessment of key and other secondary endpoints will be conducted on the FAS_ANH+, which includes adult (not elderly) participants with MDD ANH+ who were randomized to aticaprant 10 mg or placebo and took at least 1 dose of study intervention, unless otherwise specified.

5.4.1. Key Secondary Endpoint

The key secondary efficacy endpoint is the change from baseline in DARS total score at Day 43 in FAS_ANH+.

The same estimand (except the endpoint) and corresponding analyses as for the primary endpoint will be used for the key secondary endpoint.

5.4.1.1. Dimensional Anhedonia Rating Scale (DARS)

5.4.1.1.1. Definition

The Dimensional Anhedonia Rating Scale (DARS) is a 17-item self-report questionnaire that was designed to assess anhedonia in MDD, and particularly to increase scale generalizability while maintaining specificity (Rizvi 2015). Respondents provide their own examples of rewarding experiences across the domains of hobbies, social activities, food/drink, and sensory experience. Participants answer a set of standardized questions about desire, motivation, effort and consummatory pleasure with a recall period of "right now" for the examples provided. Response options for each item use a 5-point Likert scale (0=not at all, 1=slightly, 2=moderately, 3=mostly, 4=very much) and responses are summed to generate the total score (range of 0 to 68) or a subscale score (range of 0 to 16 each for pastimes/hobbies, food/drink, and social activities and 0 to 20 for sensory experiences). A lower total score is indicative of greater anhedonia.

Imputation of total score is presented in Section 5.1.3.

Positive changes in DARS total score indicate improvement.

5.4.1.1.2. Estimand(s)

The same estimand as defined for the primary endpoint in Section 5.3.2 are defined for DARS, with the variable being the change from baseline in DARS total score at Day 43 in FAS_ANH+.

5.4.1.1.3. Analysis Methods

The same analyses described for the estimand under the primary endpoint will be implemented for change from baseline in DARS total score at Day 43.

A fixed sequence testing procedure will be applied to control the family-wise error rate (FWER) at two-sided 0.05 level accounting for multiplicity due to the primary (MADRS total score) and the key secondary efficacy endpoints (DARS total score). The testing procedure will first test the primary endpoint at two-sided 0.05 level. If the hypothesis corresponding to the primary endpoint is rejected, then the key secondary endpoint will be tested at 2 sided 0.05 level; if the hypothesis corresponding to the primary endpoint is not rejected, then the testing procedure will stop.

5.4.1.1.4. Other Analyses

Descriptive statistics of the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented for DARS total score by intervention group for FAS_ANH+ and FAS_All. Change from baseline of DARS total score based on the observed data in the double-blind phase will be analyzed for FAS_All using the same MMRM model as described for the primary endpoint in section 5.3.2.1.1 along with the following additional terms in the model: ANH strata (MDDANH1, MDDANH2, MDDAH3) and age group (adult, elderly) LS mean changes from baseline (+/- SE) will be presented over time.

To assess the treatment effect in participants without anhedonia, descriptive statistics of the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented for DARS total score by intervention group for MDD_WOANH_S and MDD_WOANH_MS analysis sets.

Additionally, descriptive statistics of observed values and change from baseline over time in the subscales of the DARS (hobbies/pastimes, food/drink, social activities, and sensory experiences) and proportion of participants with response at Day 43 (defined as change from baseline in DARS total score ≥ meaningful change threshold [or range of thresholds] determined by anchor-based analyses of blinded interim data) will also be provided by intervention group for FAS_ANH+ and FAS_All. Cumulative distribution curves for change from baseline in DARS total score by study intervention will be presented for FAS_ANH+ and FAS_All (Note: The meaningful change threshold, or range of thresholds, will be finalized prior to database lock).

To address an FDA request to provide a supplementary analysis using a more direct measure to define moderate-to-severe anhedonia, analysis of change from baseline of DARS total score at Day 43 for adult participants in FAS_All will be performed in a similar manner as specified in section 5.3.2.1.1 for the following sub-populations:

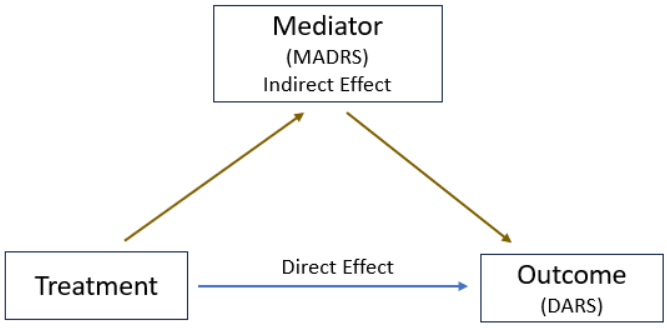
- MADRS Item 8 score (≥2, <2)

The difference of LS mean change (95% CI) at Day 43 will be presented for each sub-population in a forest plot. Additionally, descriptive summaries of change over time in DARS total score will be provided for the two sub-groups.

Mediation Analysis

A mediation analysis will be performed to examine the mediating role of change from baseline in MADRS total score at Day 43 on change from baseline in DARS total score at Day 43 provided that both endpoints demonstrate a statistically significant difference between JNJ-67953964 and placebo for FAS ANH+ under the primary estimand.

Figure 3: Meditation analysis framework



In the mediation analysis framework, natural direct effect can be conceived of as the independent treatment effect on the outcome (i.e., change in DARS total score) that is above and beyond its effect on the mediator (i.e., change in MADRS total score); controlled direct effect can be conceived of as the independent treatment effect on the outcome controlling the mediator at a fixed level; and natural indirect effect can be conceived of as a treatment effect on the outcome that is accounted for by its effect on the mediator (Figure 3).

This analysis will assess the extent to which change in DARS total score may be mediated by or independent of change in MADRS total score based on observed data (i.e., data collected at each time point without carrying forward previous values) at Day 43. The analysis will consider both change in DARS total score and change in MADRS total score as continuous variables.

Simulation-based Counterfactual Approach analysis introduced by Imai etal. (2010) obtains the natural direct effect and natural indirect effect using numerical simulations. The approach uses parametric bootstrapping to construct the point estimate and its uncertainty estimates for direct effect and indirect effect from the bootstrap sampling distribution. For each bootstrapped sample, change from baseline in DARS total score and change from baseline in MADRS total score will be analyzed. The ANCOVA analysis of change in DARS total score from baseline will include factors for intervention group (aticaprant 10 mg and placebo), country/territory, change from baseline in MADRS total score, baseline MADRS total score, treatment-by-change from baseline in MADRS total score interaction if the interaction is significant, and baseline DARS total score as a covariate. The ANCOVA analysis of change in MADRS total score will include factors for intervention group (aticaprant 10 mg and placebo) and country/territory, baseline MADRS total score and baseline DARS total score as covariates. Estimate of the controlled direct effect will be obtained by plugging in the estimated coefficient values and the mean level of change in MADRS total score into the analytic expressions.

The proposed analysis makes two important and untestable assumptions. First, the analysis is performed under the assumed causal structure shown in Figure 3, where the mediator and the outcome are measured at the same timepoint. Using cross-sectional data of this type, it is not possible to know the direction of causality (VanderWeele,2015). For example, the true causal structure may reverse the roles of mediator and outcome, where effects on anhedonia (change from baseline DARS) may mediate the effect on depressive symptoms (change from baseline MADRS). Second, to identify the natural direct and indirect effects, the analysis is performed under the standard, but untestable, assumption of sequential ignorability (Imai et al., 2010). In particular, it is assumed that the potential value of the mediator and the potential value of the outcome are independent, conditional on the treatment and any confounding variables. The impact of this second assumption will be evaluated through a sensitivity analysis as described in Tingley et al (2014).

5.4.2. Other Secondary Endpoint(s)

5.4.2.1. Response Based on MADRS Total Score

5.4.2.1.1. Definition

A participant is defined as a responder at a given time point if the percent improvement from baseline in MADRS is ≥50% at that time point (i.e., percent change ≤-50%). Participants who do not meet such criterion will be considered as non-responders. Imputation of missing response status is presented in Section 5.1.3.

5.4.2.1.2. Analysis

The number and percentage of participants who achieve a response will be summarized at each time point during the double-blind phase and follow-up phase by intervention group. The summary and graph will be provided for observed and imputed data (participants with missing values will be imputed as non- responders). This analysis will be performed for FAS_ANH+ analysis set.

The cumulative response rate, defined as the percentage of participants experiencing at least a given value of percent reduction from baseline to Day 43 in MADRS total score, will be presented graphically, for both observed and imputed data (participants with missing values will be imputed as non-responders).

5.4.2.2. Remission Based on MADRS Total Score

5.4.2.2.1. Definition

A participant is defined as a remitter at a given time point if the MADRS total score is [≤10] at that time point. Participants who do not meet such criterion will be considered as non-remitters. Imputation of missing remission status is presented in Section 5.1.3.

5.4.2.2.2. Analysis

The number and percentage of participants who achieve remission will be summarized at each time point during the double-blind and follow-up phases by intervention group. The summary and graph will be provided for observed and imputed data (participants with missing values will be imputed as non-remitters). This analysis will be performed for FAS_ANH+ analysis set.

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

5.4.2.3.1. Definition

CCI [redacted]

5.4.2.3.2. Analysis

Descriptive statistics of the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented for PHQ-9 total score and PHQ-9 anhedonia-specific item (PHQ-9, item 1) by intervention group for FAS_ANH+ and FAS_All. The proportion of participants with a score >= 2 at baseline but less than 2 in the PHQ-9 anhedonia-specific item (PHQ-9, item 1) at Day 43 will be summarized for FAS_ANH+ and FAS_All.

The change from baseline in PHQ-9 total score over time based on the observed data in the double-blind phase will be analyzed using the same MMRM model as described for the primary endpoint with baseline PHQ-9 total score as the covariate. Difference of LS means (95% CI) will be provided at each time point.

LS mean changes from baseline (+/- SE) will be presented by over time.

5.4.2.4. PROMIS Ability to Participate in Social Roles and Activities Short Form 8a (PROMIS Social Functioning)

5.4.2.4.1. Definition

CCI [redacted]

5.4.2.4.2. Analysis

Descriptive statistics of the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented for the total scores of PROMIS Social Functioning Short Form 8a and the T-score by intervention group.

The change from baseline in T-score over time in the double-blind phase will be analyzed using the same MMRM model as described for the primary endpoint with baseline T-score as the covariate. Difference of LS means (95% CI) will be provided at each time point.

LS mean changes from baseline (+/- SE) for T-score will be presented graphically over time.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

The assessment of tertiary/exploratory endpoints below will be conducted on the FAS_ANH+ and FAS_All separately, unless otherwise specified.

5.5.1.1. MADRS-6

5.5.1.1.1. Definition

CCI [redacted]

5.5.1.1.2. Analysis

Descriptive statistics of the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented for MADRS-6 total score by intervention group.

The change from baseline in MADRS-6 total score over time based on observed data in the double-blind phase will be analyzed using the same MMRM model as described for the primary endpoint with baseline MADRS-6 total score as the covariate for FAS_ANH+. Difference of LS means (95% CI) will be provided at each time point.

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

5.5.1.2. Snaith-Hamilton Pleasure Scale (SHAPS)

5.5.1.2.1. Definition

CCI [redacted]

5.5.1.2.2. Analysis

Descriptive statistics of the observed values and the change from baseline to each time point in the double-blind phase will be presented for SHAPS total score by intervention group.

The change from baseline of SHAPS total score over time based on the observed data in the double-blind phase will be analyzed using the same MMRM model as described for the primary endpoint with baseline SHAPS total score as a covariate for FAS_ANH+. Difference of LS means (95% CI) will be provided at each time point.

Frequency distributions of SHAPS individual items will be provided and plotted over time in the double-blind phase for FAS_ANH+.

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

5.5.1.3.1. Definition

CCI [redacted]

5.5.1.3.2. Analysis

Descriptive statistics of the observed values and the change from baseline will be presented at each time point in the double-blind and follow-up phases by intervention group for observed case data.

The change from baseline in CGI-S score over time based on the observed data in the double-blind phase will be analyzed using the same MMRM model as described for the primary endpoint with baseline CGI-S score as a covariate for FAS_ANH+. Difference of LS means (95% CI) will be provided at each time point.

A frequency distribution of the CGI-S scores over time will be provided by intervention group. The frequencies of CGI-S scores will be plotted at baseline and endpoint(DB) for FAS_ANH+.

5.5.1.4. Patient Global Impression of Severity (PGI-S)

5.5.1.4.1. Definition

CCI [redacted]

5.5.1.4.2. Analysis

Descriptive statistics of the observed values and the change from baseline will be presented by intervention group at each time point in the double-blind and follow-up phases for observed case data for anhedonia and depression separately.

The change from baseline in PGI-S score over time based on the observed data in the double-blind phase for anhedonia and depression will be analyzed using the same MMRM model as described for the primary endpoint with baseline PGI-S score as a covariate for FAS_ANH+. Difference of LS means (95% CI) will be provided at each time point.

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

A frequency distribution of the PGI-S dimension scores over time will be provided by intervention group for anhedonia and depression. The frequencies of PGI-S scores for anhedonia and depression will be plotted over time for FAS_ANH+.

5.5.1.5. Patient Global Impression of Change (PGI-C)

5.5.1.5.1. Definition

CCI [redacted]

5.5.1.5.2. Analysis

Descriptive statistics of the observed values at endpoint in the double-blind phase will be presented by intervention group for observed case data.

An ANOVA model will be used to analyze the PGI-C score for anhedonia at endpoint(DB) between aticaprant and placebo. The model will include the PGI-C score for anhedonia at endpoint(DB) as the dependent variable, intervention group (aticaprant 10 mg and placebo) and country/territory as factors for FAS_ANH+. Difference of LS means (95% CI) will be provided.

A frequency distribution of the PGI-C for anhedonia at endpoint(DB) will be provided by intervention group as well.

5.5.1.6. Generalized Anxiety Disorder 7-item Scale (GAD-7)

5.5.1.6.1. Definition

CCI [redacted]

5.5.1.6.2. Analysis

Descriptive statistics of the total score and change from baseline will be provided for each visit for observed data.

An ANCOVA model will be used to analyze the change from baseline in GAD-7 total score at endpoint(DB) between aticarprant and placebo for FAS_ANH+. The model will include the change from baseline at endpoint(DB) for GAD-7 total score as the dependent variable, intervention group (aticaprant 10 mg and placebo) and country/territory as factors, and baseline GAD-7 total score as a covariate. Difference of LS means (95% CI) will be provided.

5.5.1.7. Quality of Life in Depression Scale (QLDS)

5.5.1.7.1. Definition

CCI [redacted]

5.5.1.7.2. Analysis

Descriptive statistics of the total score and change from baseline will be provided for observed data.

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

5.5.1.8.1. Definition

CCI [redacted]

CCI

[redacted]

5.5.1.8.2. Analysis

Descriptive statistics of the observed values and the change from baseline to each time point in the double-blind and follow-up phases will be presented by intervention group for weighted EQ-5D health status index, the EQ-VAS, and the sum score.

Individual dimension responses will also be summarized at each visit with frequency counts and percentage of participants by intervention group. Proportion of participants with dimension scores of 2-5 (indicating any problem) will be plotted for each dimension at baseline and endpoint(DB) for FAS_ANH+.

5.5.2. Subgroup Analyses

For the subgroups listed in Section 5.7.3, subgroup analyses using MMRM will be performed for the change in MADRS total score at Day 43 for FAS_ANH+ under the primary estimand - ROW. The fixed terms in the model will be intervention group, country/territory, time, subgroup, time-by-intervention interaction, intervention-by-subgroup interaction, and time-by-intervention-by-subgroup interaction, and baseline MADRS total score as a covariate. Point estimates of the treatment differences and 2-sided 95% CI will be estimated using the appropriate contrasts. Country/territory will not be included in the model if the subgroup of interest is Region.

The analysis results (difference of LS means and 95% CI) of the different subgroups will be displayed in a forest plot.

Similar analyses will be performed for the change in DARS total score at Day 43 and the results will be displayed in a forest plot.

5.6. Safety Analyses

All safety analyses will be based on safety analysis set based on randomized intervention, unless otherwise specified.

Safety analysis will be conducted separately for the DB and follow-up 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.

5.6.1. Extent of Exposure

The number and percentage of participants who receive study intervention will be summarized.

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

Duration of study intervention will be summarized in the following categories: <=7 days, 8-14 days, 15-21 days, 22-28 days, 29-35 days, 36-42 days, >42 days.

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

Current antidepressant duration is defined as (minimum of end of double-blind study intervention and end of antidepressant use – maximum of start of double-blind study intervention and start of antidepressant use)+1.

The summaries will be provided for FAS_ANH+, MDD_WOANH_S, MDD_WOANH_MS and safety analysis set.

5.6.1.1. Compliance

Compliance will be summarized descriptively for each study intervention and the current antidepressant.

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.

Compliance will be calculated for the study intervention as:

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

Compliance will be calculated for the current antidepressant as:

Compliance (%) = (number of days actually dosed with the current antidepressant while on study intervention) / (duration of study intervention) x 100%

The summaries will be provided for FAS_ANH+, MDD_WOANH_S, MDD_WOANH_MS and safety analysis sets.

5.6.2. 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 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:

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.

Summary tables will be provided for:

- AEs (all AEs, and AEs with incidence of at least 5% in any treatment group)
- Serious AEs (SAEs)
- AEs leading to discontinuation of study intervention (DB treatment phase only)
- AEs by severity
- AEs by relationship to study intervention
- Severe AEs
- AEs of special interest
  - CCI [redacted]
- AEs of clinical interest
  - C [redacted] system organ class AEs
  - Suicide/Self-injury (First Sub SMQ)
  - AEs suggestive of abuse potential (Appendix 11)

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

- Died
- Had SAEs
- Had AEs leading to discontinuation of study intervention
- Had AEs of special interest

- Special interest AEs include [redacted]

- Had AEs of clinical interest
  - [redacted] system organ class AEs
  - 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.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Descriptive statistics will be presented for all chemistry, hematology, and urinalysis laboratory tests at scheduled time points in the double-blind phase.

Change from baseline to all post-baseline visits in the double-blind phase will be summarized for chemistry, hematology, and urinalysis tests and displayed by study intervention group.

Clinical laboratory test values collected in the double-blind phase will be considered "treatment-emergent markedly abnormal" (TEMA) using the criteria 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 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 value is missing, a postbaseline marked abnormality will always be considered as TE.

The number and percentage of participants with treatment-emergent markedly abnormal values will be presented by study intervention group. It will be conducted for all participants and separately for the participants who experience [redacted] TEAEs.

Incidence of participants with ALT values ≥ 3*upper normal limit (ULN), AST values ≥ 3*ULN, total bilirubin values ≥ 2*ULN (or at least doubling of direct bilirubin in known Gilbert's syndrome),, and international normalized ratio (INR) > 1.5 (if measured) will be presented for the double-blind phase. Additionally, incidence of hepatic toxicity (Hy's Law) defined as ALT or AST values ≥ 3*ULN AND alkaline phosphatase < 2*ULN AND (total bilirubin values ≥ 2*ULN OR international normalized ratio (INR) > 1.5, if measured) in the double-blind phase will be presented. 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 will be provided for the double-blind phase. A listing of participants with ALT ≥ 3* ULN or AST values ≥ 3*ULN) and participants with hepatic toxicity (suspected Hy's Law cases) in the double-blind phase will be provided.

5.6.3.2. 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. 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 below) will be applied to postbaseline values in the double-blind phase.

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

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

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

Incidence of treatment-emergent clinically important vital signs during intervention, as defined in Table 4, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign during the DB phase. A listing of participants with treatment-emergent clinically important abnormalities in vital signs during the DB phase will be presented, along with a listing of clinical important vital sign measurements.

Table 4: 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

5.6.3.3. 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 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.

The number and percentage of participants with QTc interval will be summarized at each time point in the double-blind phase. The number and percentage of participants with QTc interval increases from baseline to the maximum postbaseline value and each post dose time point will be summarized for double-blind phase. Refer to the following Table 5 for summary categories.

Table 5: 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

Shift table will be provided from baseline to maximum post baseline QTc interval for the double-blind phase.

Descriptive statistics of ECG parameters and change from baseline will be summarized at each scheduled time point for double-blind and follow-up phases.

Abnormality criteria (based on criteria defined in Table 6 below) will be applied to baseline and postbaseline values in the double-blind phase.

Postbaseline abnormalities will be compared with their corresponding baseline result:

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

The number and percentage of participants with treatment-emergent ECG values outside predefined limits will be presented by study intervention over time for the double-blind phase:

Table 6: 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 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.

Listings of ECG abnormalities (see Table 6) and abnormal QTc values in the double-blind phase will also be provided.

5.6.3.4. Other Safety Parameters

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

CCI

CCI [redacted]

5.6.3.4.2. Arizona Sexual Experiences Scale (ASEX)

CCI [redacted]

5.6.3.4.3. Physician Withdrawal Checklist 20-item (PWC-20)

CCI [redacted]

5.7. Other Analyses

5.7.1. Pharmacokinetics

PK analyses will be performed on the safety analysis set.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize plasma concentrations at each sampling time point and for each PK parameter of Active Study Intervention.

5.7.2. Biomarkers

Analysis of biomarker data will be discussed in a separate SAP.

5.7.3. Definition of Subgroups

Subgroup analyses of the primary and key secondary endpoints will be performed for the FAS_ANH+ analysis sets for the following subgroups:

- Sex (male, female, unknown, undifferentiated)
- Race (Black or African American, White, Other, Not Reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- Country/territory
- Region (south America, north America, Europe, other)
- Age Group (18-44 years, 45-64 years)
- 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)
- Number of major depressive episodes (1, 2-5, 6-10, >10)
- Curent antidepressant type (SSRI, SNRI)
- Baseline MADRS (≤/> median)
- Baseline DARS (≤/>median)

- Benzodiazepine (Yes, No)
- SCID-CT With melancholic features (Yes, No)
- SCID-CT With anxious distress (Yes, No)

5.8. Interim Analyses

A blinded interim analysis will be performed to evaluate the measurement properties of the DARS, and to determine meaningful change threshold (MCT) (or range of thresholds) in the DARS total score using anchor-based approaches along with distribution-based analyses. The interim analysis will be conducted when approximately 200 adult MDD participants, regardless of anhedonia status, have completed the DB Treatment Phase of the study. Details of the analysis will be described in a separate analysis plan.

5.8.1. Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be commissioned to periodically review safety data for this study. Details about the membership of the IDMC and its roles and responsibilities are discussed in a separate IDMC charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AE	Adverse event
AESI	Adverse event(s) of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ASEX	Arizona Sexual Maturity Scale
AST	Aspartate aminotransferase
ATC	Anatomic and therapeutic class
BMI	Body mass index
C-SSRS	Columbia suicide severity rating scale
CGI-S	Clinical global impression-severity
CI	Confidence interval
CIR	Copy increment from reference
CR	Copy reference
CRF	Case report form
CV	Coefficient of variation
DARS	Dimensional anhedonia rating scale
DB	Double-blind
DPS	Data Presentation Specifications
DSM-5	Diagnostic and statistical manual of mental disorders, 5th edition
ECG	Electrocardiogram
EQ-5D-5L	European quality of life, 5-dimension, 5-level
EQ-VAS	European quality of life-visual analog scale
EU	European union
FAS_All	Full analysis set (All)
FAS_ANH+	Full Analysis Set (ANH+)
FU	Follow-up
FWER	Familywise error rate
GAD-7	Generalized anxiety disorder 7-item scale
GI	Gastrointestinal
HSI	Health status index
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
MCMC	Markov chain monte carlo
MCT	Meaningful change threshold
MDD	Major depressive disorder
MDD ANH+	MDD with moderate-to-severe anhedonia
MDD ANH-	MDD without moderate-to-severe anhedonia
MDD_WOANH_MS	MDD without anhedonia CCI [redacted]
MDD_WOANH_S	MDD without anhedonia CCI [redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
NSAIDs	Non-steroidal anti-inflammatory drugs
non-PAP	Non primary analysis population
PGI-C	Physician Global Impression-Change
PGI-S	Physician Global Impression-Severity
PHQ-9	Patient Health Questionnaire-9 Item
PK	Pharmacokinetic(s)
PWC-20	Physician Withdrawal Checklist 20-items
QLDS	Quality of life in depression scale
ROW	Rest of the world

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

The analysis of exploratory endpoints on the MDD ANH- population (now referred to as non-PAP) stated in the protocol will not be performed as this population contains participants with prominent anhedonia CCI [redacted] However, these participants will be included in the All MDD population.

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 7 presents a list of the demographic variables that will be summarized by intervention group and overall for the FAS_ANH+, MDD_WOANH_S, MDD_WOANH_MS and safety analysis sets.

Table 7: 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: 18-44, 45-64, 65-74	
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, Asia, 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, 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.

Table 8 presents a list of the baseline disease characteristics variables that will be summarized by intervention group and overall for the FAS_ANH+, MDD_WOANH_S, MDD_WOANH_MS and safety analysis sets.

Table 8: 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 SHAPS total score	
Baseline DARS total score	
Baseline CGI-S score	
Baseline PGI-S score: anhedonia	
Baseline PGI-S score: depression	
Baseline PHQ-9 total score	
Baseline HDRS-17 total score	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
Number of major depressive episodes (1, 2-5, 6-10, >10)	
Current antidepressant type (SSRI/SNRI)	
Number of previous prior antidepressants (0, 1, 2, 3, >3)	
Number of classes of previous ADs received prior to the current AD	
Presence of [redacted] Medical History (Yes, No)	
Baseline CGI-S score (Normal (not at all ill), Borderline mentally ill, Mildly ill, Moderately ill, Markedly ill, Severely ill, Among the most extremely ill patients)	
Screening C-SSRS category (no event, suicidal ideation, suicidal behavior)	
SCID-CT DSM-5 MDD specifiers for MDD	
[redacted]	
Baseline PGI-S score: anhedonia (None, Mild, Moderate, Severe, Very severe)	
Baseline PGI-S score: depression (None, Mild, Moderate, Severe, Very severe)	
Overall Severity of Anhedonia	
Mild	
Moderate	
Severe	
Very severe	
Family history of	
Alcohol Abuse (Yes, No)	
Anxiety Disorder (Yes, No)	
Bipolar Disorder (Yes, No)	
Depression (Yes, No)	
Schizophrenia (Yes, No)	
Substance Abuse (Yes, No)	
Tabacco usage (Yes, No)	

* 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 FAS_ANH+ 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.

If deemed necessary, additional analyses of protocol deviations for assessing and mitigating the impact of COVID-19 on study outcome will be conducted as presented in Appendix 9**.**

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 double-blind and follow-up phases for safety and follow-up 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]
Non-steroidal anti-inflammatory drugs (NSAIDs)
Medications for treatment of CCI [redacted]
Medications for treatment of CCI [redacted]

6.7. Appendix 7 Conversion of Raw Score to T-Score for PROMIS

Ability to Participate Social 8a *Short Form Conversion Table*		
Raw Score	**Scale Score**	**SE***
8	25.9	3.9
9	29.7	2.3
10	31.3	1.9
11	32.6	1.7
12	33.6	1.6
13	34.5	1.6
14	35.3	1.5
15	36.2	1.5
16	36.9	1.5
17	37.7	1.5
18	38.5	1.5
19	39.3	1.6
20	40.2	1.6
21	41.1	1.6
22	42.0	1.7
23	43.0	1.7
24	44.0	1.7
25	45.0	1.7
26	46.0	1.6
27	47.0	1.6
28	48.0	1.6
29	48.9	1.6
30	49.9	1.6
31	50.8	1.6
32	51.7	1.6
33	52.7	1.6
34	53.6	1.6
35	54.6	1.6
36	55.7	1.6
37	56.8	1.7
38	58.2	2.0
39	60.2	2.5
40	65.4	4.9
*SE = Standard Error on T-score metric		

Adult version

6.8. Appendix 8 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

6.9. Appendix 9 Analyses for Assessing and Mitigating the Impact of COVID-19 on Study Outcome

The following measures will be taken to handle the impact of COVID-19 on study outcome:

1. Listing and summary of treatment discontinuation and study discontinuation including reasons due to COVID-19 will be presented.

2. Protocol deviation related to COVID-19 including missing visits and remote visits due to COVID will be summarized; corresponding listing will be provided.

3. Additional analyses to assess the potential impact of COVID-19 in the primary and key secondary endpoints.

    a. Mean summaries over time by types of collection (remote, home, site, etc).

    b. Sensitivity analyses will be provided by including types of collection in the primary models for MADRS and DARS.

4. Sensitivity analysis for the primary Estimand - ROW: Additional tipping point analysis will be performed for the primary Estimand - ROW where the delta adjustments will be applied to missing data under hypothetical strategy including those caused by discontinuation reasons due to COVID- 19; delta adjustments will not be applied to data due to discontinuation reasons not related to study intervention including Lost to Follow-Up, Withdrawal by Subject or Other.

Note: The above measures will be taken in instances where a large number of COVID infections are reported. A few isolated cases of COVID-19 infection reported by the participants will not warrant the above analyses.

6.10. Appendix 10 Delta Adjustment Multiple Imputation

1. If the data has non-monotone missing data, then impute any intermediate missing data with Markov Chain Monte Carlo method.

```
/*visits v1-v3 are corresponding to Day 15, 29 and 43 for MADRS, trt=2 is for control group*/
proc mi data=MADRS_data nimpute=500 seed=1234 out=MADRS_mcmc noprint;
  var treatment baselinecountry/territory v1-v3;
  mcmc chain=single nbiter=200 niter=100 impute=monotone;
proc sort;by _imputation_;
run;
```

2. Delta adjustment

```
%macro procmib_deltamar(indata=,deltac=,deltad=);
    data indata_mi;
      set MADRS  mcmc;
       v1_mi=v1;v2_mi=v2;v3_mi=v3;
    run;
/*Perform MI with monotone regression method*/
/*As multiple datasets have been already created with MCMC, use only nimpute=1*/
/*If original dataset has monotone missing data, use nimpute>1 such as 500*/
    proc mi data=indata_mi out=reg nimpute=1 seed=123 noprint;
      by _imputation_;
       var trt base v1_mi v2_mi v3_mi;
       class trt;
       monotone regression;
    run;

   data regd;
     set reg;
       if trt=1 then do;
         if v1=. then v1_mi=v1_mi-&deltac;
         if v2=. then v2_mi=v2_mi-&deltac;
         if v3=. then v3_mi=v3_mi-&deltac;
       end;
       if trt=2 then do;
         if v1=. then v1_mi=v1_mi+&deltad;
         if v2=. then v2_mi=v2_mi+&deltad;
         if v3=. then v3_mi=v3_mi+&deltad;
       end;
   run;

  data regsd;
      set regd;
       c1_mi=v1_mi-base;c2_mi=v2_mi-base;c3_mi=v3_mi-base;
  proc sort data; by _imputation;
```

```
 run;

%mend;
%procmib_deltamar(indata=MADRS_mcmc,deltac=0,deltad=1);
```

3. Analyze fully imputed datasets with MMRM

```
data MADRS_reg_subset;
  set regsd;
  keep _imputation_ ID Country trt base c1_mi c2_mi c3_mi;
 run;
 proc sort data=MADRS_reg_subset;
       by ID Country trt base _imputation_;
  run;

 proc transpose data=MADRS_reg_subset
                  out=MADRS_mi_vertical  name=visit prefix=change;
        by ID Country trt base _imputation_;
 run;

data MADRS_mi_vertical;
   set MADRS_mi_vertical;
      rename change1=change;
      if visit="c1  mi" then visitn=1;
      if visit="c2_mi" then visitn=2;
      if visit="c3_mi" then visitn=3;
 proc sort;by _imputation_ ID visitn;
 run;

 proc mixed data=MADRS_mi_vertical;
           by _imputation;
           class  trt Country visitn id ;
           model change  = base trt Country visitn trt*visitn /ddfm=kr;
           repeated visitn / sub = id type = un;
           lsmeans trt*visitn/ diff=control('2' '3');
           ods output lsmeans=lsm_mib diffs=diff_mib;
  run;
```

4. Pool the results with Rubin's rules

```
 proc mianalyze parms=diffmi;
      class trt visitn;
      model effects treatment; /* check to see what MMRM outputs to determine which
variables to include */
      ods output parameterestimates=diffmian;
  run;
```

6.11. Appendix 11 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:

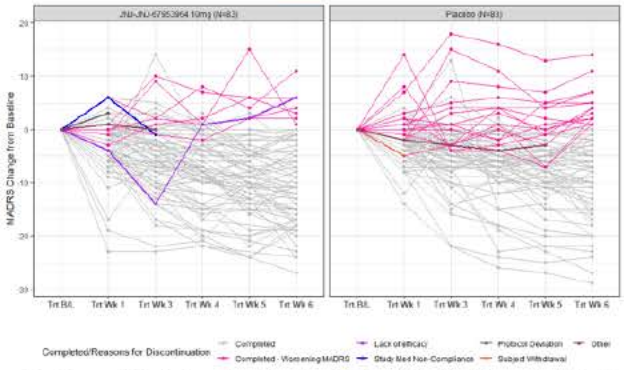
  Dopamine dysregulation syndrome; Drug abuse; Drug abuser; Drug dependence; Drug dependence, antepartum; Drug dependence, postpartum; Drug use disorder; Drug use disorder, antepartum; Drug use disorder, postpartum; Intentional overdose; Intentional product misuse; Maternal use of illicit drugs; Neonatal 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

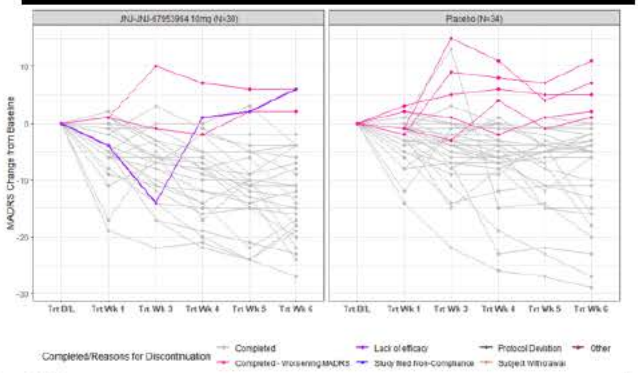
6.12. Appendix 12 Spaghetti Plot of MADRS Change Over Time (Study 67953964MDD2001)

Change in MADRS Total Score by Reason for Discontinuation from the Study (MDD2001)

All fITT Subjects



CCI



1. The overall study discontinuation rates (fITT analysis set): Aticaprant: 4.8%, Placebo: 2.4%

CCI 1 aticaprant subject discontinued the study during the 2-week placebo run-out period (lack of efficacy) after completing the 6-week treatment period. This subject took aticaprant for 43 days.

3. There is no discernable difference in the trajectories between those who discontinued and the completers. The trajectories of MADRS change in subjects who **competed the study but had a worsening of score at Week 6** (pink lines) don't appear to be very different from the **subject who discontinued the study due to lack of efficacy** (purple line)

Conclusion: There is insufficient information to conclude that there is a difference in the MADRS trajectories among completers compared to those who discontinued the study.

fITT: All enrolled subjects who were randomized into a treatment period, received at least one dose of study medication in the treatment period and have at least one post-treatment baseline assessment of MADRS during the treatment period.

6.13. Appendix 13 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.

6.14. Appendix 14 Scoring of QLDS items

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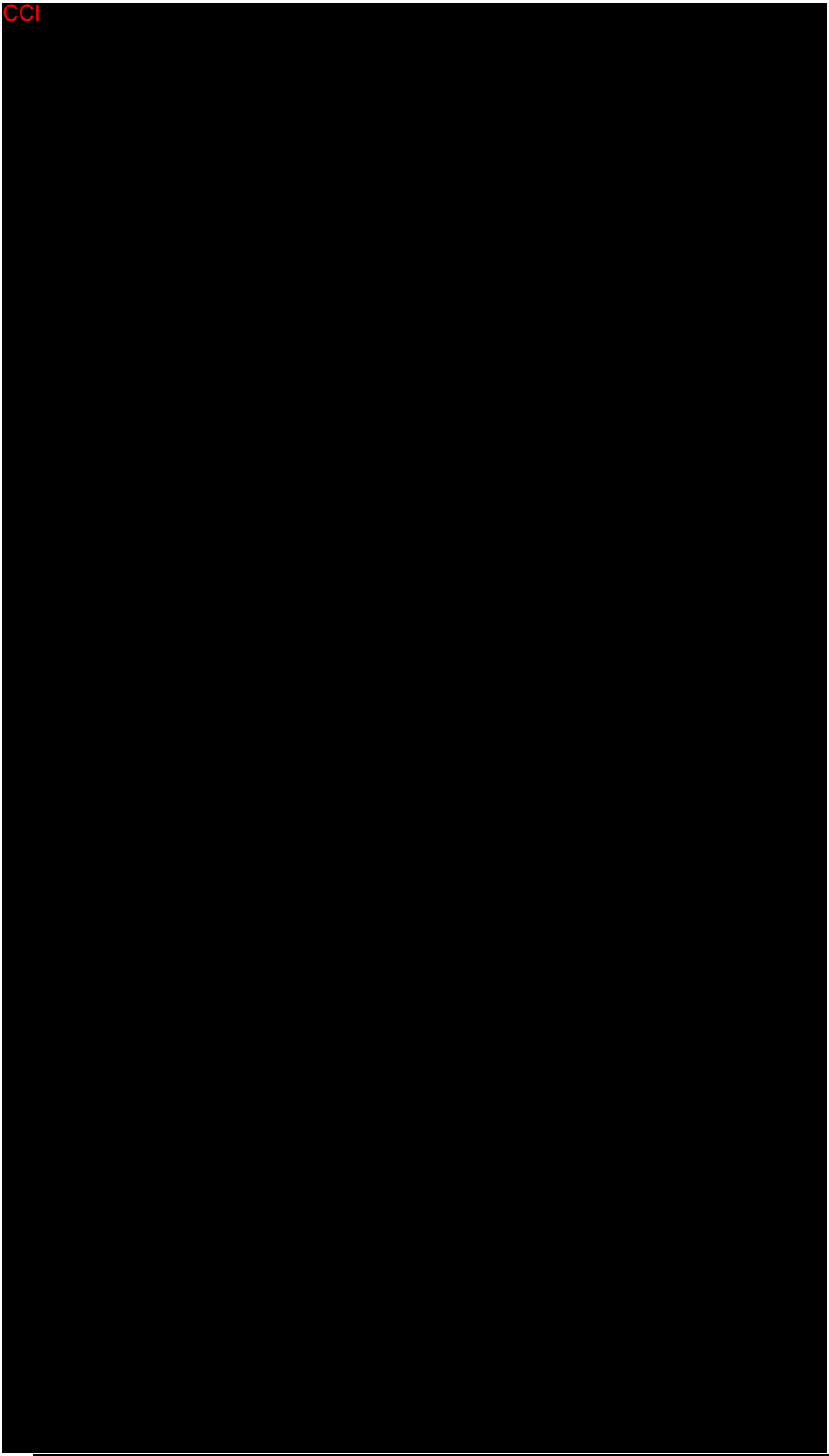

CCI

[redacted]

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