Janssen Research & Development *

Clinical Protocol

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 VENTURA-2; Phase 3
Version: Amendment 1

JNJ-67953964 Aticaprant

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Studies conducted at sites in the United States (US) will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Regulatory Agency Identifier Numbers:
IND: 111006
EudraCT NUMBER: 2022-000461-41

Status:	Approved
Date:	22 February 2023
Prepared by:	Janssen Research & Development, LLC
EDMS number:	EDMS-RIM-621368, 2.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	22-Feb-2023
Original Protocol	12-Aug-2022

Amendment 1 (22-Feb-2023)

Overall Rationale for the Amendment: Updates are made based on feedback received from interactions with health authorities, to ensure alignment across the program and to improve participant selection. Minor changes are made throughout the protocol for clarification and to correct errors.

The changes made to the clinical protocol 67953964MDD3002 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis, Overall Design; 4.1.2. Screening Phase; 5.1. Inclusion Criteria	Revised Inclusion Criterion 5: Have had an inadequate response to at least 1 ~~but no more than 3 antidepressants~~ **oral antidepressant treatment** (see the inclusion criterion below), administered at an adequate dose **(at or above the minimum** therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current episode of depression. An inadequate response is defined as <50% reduction **in depressive symptom severity** but with some improvement **(> 0%)** ~~during the current antidepressant trial~~ (ie, there may be **minimal** ~~some minor~~ 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. ~~An adequate duration is defined as an antidepressant treatment for at least 6 weeks on a stable dose at or above the minimum therapeutic dose specified in the MGH ATRQ.~~ This must ~~also~~ apply to the participant's current antidepressant treatment.	Definition for inadequate response to the current antidepressant (SSRI/SNRI) is updated based on major Health Authority feedback to include MDD participants with >0% to <50% improvement to the current antidepressant based on the MGH ATRQ criteria for amount (%) of improvement. The updates allow inclusion of a broader MDD population for whom an add-on strategy is considered a viable treatment option following inadequate response to a standard of care antidepressant. Additionally, the upper limit of up to 3 inadequate antidepressants is removed to allow enrolment and evaluation of adjunctive aticaprant in MDD participants with inadequate response to later lines of antidepressants.
1.1. Synopsis, Objectives and Endpoints; 3. Objectives and Endpoints	Revised definition of remission of depressive symptoms to a MADRS total score of ≤10.	Update made to align with the more commonly used cut off for defining remission using MADRS total score.
1.1. Synopsis, Statistical Methods, Number of Participants; 1.2. Schema; 4.1. Overall Design; 9.2. Sample Size	Revised language with regards to China and Japan's participation in the study: Additionally, approximately 118 participants from China ~~and/or 54 participants from Japan~~ will participate in the study. **In the event**	To allow for flexibility in study execution in Japan.

Section Number and Name	Description of Change	Brief Rationale
Determination; 9.4.1. General Considerations	**Japan participates in the study, approximately 54 participants will be enrolled in this country/territory.** The details will be described in the respective country/territory-specific amendments to the protocol. Data from China and Japan **(if participating)** will be combined with the global data for local registration in the respective countries/territories.	
2.2. Background	Additional information added to Human Pharmacokinetics.	To add new information from completed clinical pharmacology studies.
3. Objectives and Endpoints; 9.4.5.3 Biomarker Analyses	Added clarifying text to exploratory digital biomarkers and related statistical analyses.	Clarification of analyses.
5.1. Inclusion Criteria	Revised Inclusion Criterion 6: Is currently receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms at screening, in any **approved** formulation and available in the participating country/territory: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine at a stable dose (at **or above the minimum** ~~a~~ therapeutic dose per MGH ATRQ) for at least 6 weeks. ~~and with some minor to moderate symptomatic improvement (>25%).~~ The current antidepressant cannot be the first antidepressant treatment for the first lifetime episode of depression.	Clarification made to improve understanding of the definition of "stable dose" for the current SSRI/SNRI antidepressant. Some text is removed as the information is captured in Inclusion Criterion 5.
5.2. Exclusion Criteria	Revised Exclusion Criterion 1 to exclude participants who have had no response/treatment failure to 5 or more antidepressant treatments (including the current SSRI/SNRI).	Criterion is updated following feedback from a major Health Authority to broaden the study population and ensure exclusion of participants with a level of treatment resistance that are unlikely to benefit from an adjunctive treatment strategy.
5.2. Exclusion Criteria	Revised Exclusion Criterion 5 to exclude participants with an inadequate response to adequate course of intravenous or intranasal ketamine or esketamine; electroconvulsive therapy (ie, at least 7 treatments), vagal nerve stimulation, or deep brain stimulation device during the current episode.	Criterion is updated to better align with the study population and ensure exclusion of participants with non-response to treatment strategies in the ongoing episode who are unlikely to benefit from an adjunctive treatment strategy.
5.2 Exclusion Criteria	Revised Exclusion Criterion 9: •During screening, a QT interval corrected according to Fridericia's formula (QTcF): [3]≥450 msec (males); ≥470 msec (female participants).	To correct a typographical error.

Section Number and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Revised Exclusion Criterion 12: Added clarifying text to specify on-site drug testing and clarify retesting is only permitted for stated reasons. Added text to clarify that a positive test for both cannabis and/or alcohol can lead to participant exclusion for the study.	To improve understanding of this criterion.
1.1. Synopsis, Objectives and Endpoints; 3. Objectives and Endpoints	Revised safety endpoint for ASEX to proportion of participants with clinically relevant sexual dysfunction.	To align the endpoint with the approach that the instrument developer recommends for analysis of the ASEX and to provide better analysis for assessment of presence or absence of sexual dysfunction.
1.1. Synopsis, Statistical Methods, Efficacy Analysis 9.4.1. General Considerations	Aligned definition of the full analysis set (FAS_ANH+) with text in Section 9.3.	Consistency with Section 9.3.
1.1. Synopsis, Statistical Methods	Added text describing the interim analysis.	For completeness and consistency with Section 9.5.
1.3. Schedule of Activities	Removed row in Screening/Administrative section for diary for current antidepressant compliance.	Removal of duplicate entry; schedule for diary completion is listed under Ongoing Review.
1.3. Schedule of Activities	Removed Pharmacogenomic and Epigenetic (DNA, RNA) Assessments at Visit 2.3 (Day 15) and Visit 2.5 (Day 29).	Removal of assessments added in error in the initial protocol version.
1.3 Schedule of Activities	Added text to Note to clarify that at Visit 2.1 (Day 1), PROs, MADRS, CGI-S, and C-SSRS must be completed prior to dosing.	To provide clarification for assessments to be completed prior to dosing.
1.3. Schedule of Activities	Added assessment at Visit 2.7 (EOT/EW) under evaluation current antidepressant compliance.	To add a missing assessment.
1.3. Schedule of Activities 3.0. Objectives and Endpoints	SHAPS assessments were added at Visits 2.3 (Day 15), 2.5 (Day 29), and 3.1 (Follow-Up).	To match with the DARS.
1.3. Schedule of Activities, footnote “w”	Added footnote “w” to specific study procedures and assessments at Visit 2.1 (Baseline).	To clarify that these study procedures and assessments must be performed before randomization
1.3. Schedule of Activities, Footnote “o”; 5.1. Inclusion Criteria, Criteria 5 and 6; 6.8.1. Current (SSRI/SNRI) Antidepressant Therapy	Added instructional text to clarify methods to confirm compliance to current antidepressant treatment during screening and the DB Treatment Phase.	To provide further clarity to the sites about acceptable means of evaluating during study compliance to the current antidepressant treatment (SSRI or SNRI).
8.1.2. Efficacy Assessments 3.0. Objectives and Endpoints	Added “anhedonia” to PGI-C.	Alignment edit.
1.3 Schedule of Activities	Replaced “video” teleconferencing with “audio” teleconferencing for HDRS-17.	To correct an error.

Section Number and Name	Description of Change	Brief Rationale
2.1. Study Rationale; 4.2.1. Study Population	Removed "core" from text describing symptoms persisting in participants treated with current antidepressants.	To align text with DSM-5 criteria.
3.0. Objectives and Endpoints	Revised exploratory endpoint for GAD-7 from change from baseline over time to change from baseline at Day 43.	The GAD-7 is only collected at baseline and at Day 43.
4.1.3. Double-blind Treatment Phase; 4.1.5. Open-label Long-term Safety Study; 6.4. Study Intervention Compliance	Clarifications were made regarding missed doses and non-compliance with study intervention.	Missed doses due to temporary interruption for clinically relevant reasons (eg, adverse event, etc) are not considered non-compliance with the study intervention.
4.2.3. Study-Specific Ethical Design Considerations; 8. Study Assessments and Procedures	Updated blood volume to be collected from each participant.	Blood volume collected in study updated to include samples for antidepressant compliance and volume of tube for DNA sample.
6.2. Preparation/Handling/ Storage/Accountability	Deleted duplicate template text.	To remove duplication.
6.3. Measures to Minimize Bias: Randomization and Blinding	Modified the statement on the number of randomization lists that will be generated.	Generalized the statement as the number of lists may further be refined to provide the opportunity to analyze other definitions of anhedonia.
6.8. Concomitant Therapy	Revised text to clarify the 6 months prior to Screening applies to all of the listed medications.	To clarify recording the medications used in past 6 months.
7.1. Discontinuation of Study Intervention	Removed 2 reasons for discontinuation of study intervention related to noncompliance with study intervention. Revised criteria for discontinuation of study intervention to align Phase 3 studies.	These 2 reasons are removed as reasons for discontinuation because study participants will not be automatically withdrawn if they discontinue study intervention before the end of the DB Treatment Phase. To provide consistency across the Phase 3 studies.
8. Study Assessments and Procedures	Added clarifying text for order of completion for PRO assessments.	Added for consistency across Phase 3 studies.
8. Study Assessments and Procedures	Added additional 12-lead ECG at Visit 2.7 (EOT/EW)	To align with assessments shown in the SoA.
8. Study Assessments and Procedures	Removed duplicate text.	To remove duplication.
8.1.2.4. Clinical Global Impression-Severity (CGI-S)	Added a statement describing rater separation.	To clarify that efficacy raters who perform the CGI-S will not be involved in assessing AEs.
1.3. Schedule of Activities, Footnote "n"; 8.2.3 Electrocardiograms	Added text to clarify that triplicate ECGs are only required during screening or at Visit 2.1. if the QTcF is prolonged on the initial ECG or during the DB Treatment Phase in case of abnormality.	To clarify when triplicate ECGs are required.
8.2.6. Columbia Suicidality Severity Rating Scale (C-SSRS)	Corrected time to be recorded in the eCRF for suicidal ideation and/or suicidal behavior at screening.	Suicidal ideation in the past 3 months and/or suicidal behavior in the past 6 months are being collected in the eCRF.

Section Number and Name	Description of Change	Brief Rationale
8.2.6. Columbia Suicidality Severity Rating Scale (C-SSRS); 11. References	Added reference for the C-SSRS.	To add missing reference.
8.2.7. Arizona Sexual Experiences Scale (ASEX)	Revised description of the ASEX to align with the revised safety endpoint.	Alignment edits.
8.3.6. Adverse Events of Special Interest	Deleted text related to moderate/severe AESI in the reporting instructions.	To clarify that all AESI are to be reported and additional information will be collected on all cases.
8.4.1. Speech/Facial Digital Biomarker Analysis	Added facial digital biomarker analysis.	To include facial digital biomarker analysis.
8.4.2. Reward Learning Task (RLT)	Added learning rate and reward sensitivity to list of measures of the RLT.	To add missing measures.
9.3. Participant Analysis Sets	Revised "Enrolled" to "All Participants" in the table describing analysis sets.	To clarify that the term 'All Participants' pertains to all screened participants while 'Enrolled' pertains to randomized participants.
9.4.5.3. Biomarker Analyses	Revised description of digital biomarker analyses.	To clarify digital biomarker analyses.
10.2. Appendix 2: Clinical Laboratory Tests	Revised bullet 3 under Other Tests (at Screening, Baseline, or During Treatment) to clarify that in some countries a urine or blood sample may be collected to assess compliance with current antidepressant medications.	To clarify that this sample is not required.
10.3.5. Long-term Retention of Samples for Additional Future Research	Added a sentence to define the start of the retention period.	To clarify when the long-term retention period begins.
10.4.3.1. Guidance for Assessing Severity of Adverse Events of Special Interest	Added a new appendix to provide guidance to investigators for assessing the severity of AESI.	To provide recommendations to consider when assessing the severity of CCI [redacted]
10.5. Appendix 5: Contraceptive and Barrier Guidance	Removed footnote "b" from "implantable progestogen-only hormone contraception associated with inhibition of ovulation" and "combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation."	Footnote b is not relevant to these examples.
10.7. Appendix 7: Prohibited Concomitant Therapies	Added barbiturates to list of prohibited therapies and removed anxiolytics except buspirone.	To clarify that barbiturates are not permitted. To clarify that some anxiolytics are permitted, but buspirone remains a prohibited medication.
10.9.2. Guidance Specific to this Protocol	Revised bullet for missed doses to remove reference to removal of dosing form.	To correct the procedure for recording missed doses due to COVID-19.
1.1. Synopsis, Statistical Methods, Overall Design; 1.1. Synopsis, Benefit-Risk Assessment; 1.1. Synopsis, Statistical Methods; 1.3. Schedule of Activities;	Minor text edits and clarifications were made for alignment.	To provide consistency within the document.

Section Number and Name	Description of Change	Brief Rationale
2.3.1. Benefits for Study Participation; 3.0 Objectives and Endpoints; 4.1. Overall Design; 4.1.3. Double-blind Treatment Phase; 4.2.1. Study Population; 4.2.4. Biomarker Sample Collection; 4.4. End of Study Definition; 6.1. Study Intervention(s) Administered; 6.3. Measures to Minimize Bias: Randomization and Blinding; 7.2. Participant Discontinuation/Withdrawal from the Study; 8.8. Pharmacogenomic and Epigenetic (DNA, RNA) Assessments; 8.9. Participant Medical Information Prior to, During and After the Study (Optional Real-world Data Collection); 9.4.5.3. Biomarker Analyses 9.4.5.7. Pharmacogenomic Analyses; 10.7. Appendix 7: Prohibited Concomitant Therapies		
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

TABLE OF CONTENTS

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

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.

An increased understanding of the neurobiology of mood disorders allows for targeted research and focus on specific brain circuits implicated in mood. This provides an opportunity for developing improved treatments of mood disorders which are informed by the underlying neurobiology. Existing evidence implicates the dynorphin opioid neuropeptide system in the regulation of mood. Kappa opioid receptor (KOR) activation by the endogenous dynorphin induces stress and depressive symptoms in humans and animals and downstream results in decreased dopaminergic function in different brain areas. It is hypothesized that selective modulation of the KOR would result in improvement of residual symptoms of depression, including behaviors involving anhedonia, by restoring normal dopamine transmission in the brain's reward/motivation circuitry. Preclinical evidence supports the therapeutic potential of KOR antagonism for the treatment of anhedonia, depression, and anxiety. Based on an emerging body of scientific evidence, selective KOR antagonism may provide therapeutic benefit in the treatment of major depressive disorder (MDD).

Aticaprant (JNJ-67953964) is a once daily, highly selective KOR antagonist, with demonstrated selectivity over mu opioid receptor (MOR) and delta opioid receptor (DOR). Aticaprant is generally well tolerated, with no clinically significant adverse events (AEs), no clinically meaningful changes and abnormalities in vital signs, laboratory evaluations or electrocardiograms (ECGs) reported. AEs of special interest include CCI

The present study is being conducted to investigate the antidepressant effect of 10 mg daily aticaprant (versus placebo) in participants (18 to 74 years, inclusive: including adult participants [18 to 64 years of age, inclusive] and elderly participants [65 to 74 years of age, inclusive]) with MDD and particularly in those with MDD with moderate-to-severe anhedonia (ANH+), who have had an inadequate response to standard-of-care antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI)/serotonin-norepinephrine reuptake inhibitor (SNRI). The change in the MADRS total score from baseline (ie, Day 1, pre-randomization, and hereafter referred to as 'baseline') to Day 43 (ie, at the end of the Double-blind [DB] Treatment Phase) in participants with MDD ANH+, as assessed using the Structured Interview Guide for the MADRS [SIGMA]), will be utilized for primary assessment of efficacy.

BENEFIT-RISK ASSESSMENT

There is evidence to suggest that with its targeted mechanism of action the selective KOR antagonism may result in improvement of symptoms of depression linked to impaired functioning in the reward circuitry (like anhedonia and amotivation) and which are poorly addressed by the current standard-of-care SSRIs/SNRIs. Presence and persistence of symptoms like elevated anhedonia predict poor outcome and chronic course of the disease. Available data from nonclinical and clinical studies (Phase 1 and Phase 2 studies) with aticaprant support the scientific and clinical rationale for the use of selective KOR antagonists in the treatment of depression with moderate-to-severe anhedonia. Data from the Phase 2 study 67953964MDD2001 showed greater reduction in overall depression severity on the MADRS in participants with MDD treated with aticaprant added to ongoing antidepressant with inadequate response, compared with those who continued their current antidepressant plus placebo. The magnitude of the overall antidepressant efficacy was different when examined based on the presence and severity of anhedonia defined using an established self-reported assessment (SHAPS) for severity of anhedonia. When treated with aticaprant, participants with a high level of anhedonia at entry, showed greater improvement of overall depressive symptoms compared with those with a low level of anhedonia. To date in clinical trials,

aticaprant was generally safe and well tolerated. Participants in this study will help in evaluating the use of aticaprant in the treatment of MDD and specifically in MDD with moderate-to-severe anhedonia, and in increasing our understanding of the disease indication. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering from MDD with moderate-to-severe anhedonia and offers potential public health benefits.

Participants may also experience some benefit from the participation in a clinical study irrespective of receiving study intervention, due to regular visits and assessments monitoring their overall health.

Study 67953964MDD3002 is the second Phase 3 study investigating the therapeutic efficacy of adjunctive aticaprant therapy in patients with MDD with moderate-to-severe anhedonia who have had an inadequate response to standard-of-care antidepressant treatment with an SSRI/SNRI. Therefore, the benefit-risk profile of adjunctive aticaprant therapy in this patient population has not been fully established.

The currently available data, and the aticaprant Investigator's Brochure (IB) support this clinical study that investigates the efficacy, safety and tolerability of aticaprant as adjunctive therapy in adult (18 to 64 years, inclusive) and elderly (65 to 73 years, inclusive) participants with MDD ANH+ who have had an inadequate response to antidepressant therapy with a SSRI/SNRI in the current depressive episode.

The scientific and clinical evidence (clinical pharmacology data, receptor occupancy modeling, safety database and efficacy data from Phase 2) supports 10 mg/day as a safe dose that would provide optimal efficacy in adjunctive treatment, where the ultimate goal is to adequately manage the remaining symptoms and undertreatment is not desirable. This short-term Phase 3 study will therefore assess a dosage of 10 mg/day for efficacy as part of the primary analysis.

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with aticaprant are justified by the anticipated benefits that may be afforded to participants; this supports further clinical investigation of adjunctive treatment with aticaprant for MDD in patients with moderate-to-severe anhedonia.

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.

Objectives	Endpoints
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) • Response of depressive symptoms (clinician-reported) • Remission of depressive symptoms (clinician-reported)	• Change from baseline over time in the MADRS total score. • Proportion of responders on depressive symptoms scale, defined as a ≥50% improvement in MADRS total score from baseline to Day 43. • Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤10 at Day 43.
• 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.	• Adverse events (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.

Objectives	Endpoints
Clinical Pharmacology Assessments	
• To assess the pharmacokinetics (PK) 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 AEs.	

Hypothesis

The hypothesis for this study is that adjunctive treatment with aticaprant 10 mg is superior to placebo in treating depressive symptoms, as measured by change in MADRS total score from baseline to Day 43 in adult participants with MDD ANH+ who have had an inadequate response to treatment with an SSRI/SNRI.

OVERALL 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 MDD with moderate-to-severe anhedonia (MDD ANH+), adult participants who do not have moderate-to-severe anhedonia (MDD ANH-), and elderly participants (65 to 74 years of age, inclusive) with MDD (ANH+ and ANH-). All participants must have had an inadequate response to an SSRI/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.

Participants will be randomized in a 1:1 ratio to receive aticaprant 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 (at or above the minimum 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%; ie, 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. A Site Independent Qualification Assessment will assess the validity of the participants' diagnosis and antidepressant treatment response for inclusion in the study.

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 (Visit 2.7), including the MADRS assessment at the end of the 6-week DB Treatment Phase (ie, Day 43 MADRS), and have not discontinued study intervention early during the DB Treatment Phase.

Participants who have completed the DB Treatment Phase (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 (Visit 3.1) 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 (Visit 3.1), including the MADRS, DARS, and PWC-20 assessments at this visit.

Participants who discontinue study intervention early (ie, prior to completion of Day 43 visit) or who are non-compliant to the study intervention (ie, 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 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 (eg, paper assessments replaced by electronic assessments and vice versa). In addition, site visits may be replaced with telephone, internet-based videoconferencing applications, or home visits by qualified health care 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.

NUMBER OF PARTICIPANTS

Approximately 538 participants[a], including adult (18 to 64 years of age, inclusive) and elderly (65 to 74 years of age, inclusive) will be enrolled in this study. This includes approximately 324 adult participants with MDD ANH+, 106 adult participants with MDD ANH-, and 108 elderly participants with MDD ANH+/MDD ANH-) that will be enrolled in this study.

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 will be described in the respective country/territory-specific amendments to the protocol.

Criteria defining MDD ANH+ and MDD ANH- subgroups are blinded to the sites and provided in an addendum to the study protocol.

INTERVENTION GROUPS AND DURATION

The assigned study intervention (aticaprant 10 mg or placebo) will be self-administered by the participant at home once daily, around the same time and preferably in the morning during the DB Treatment Phase. When participants visit the site, study intervention should be taken at the site and witnessed by the investigator or a properly trained designee. The maximum duration of participation in the study for an individual participant (including Screening, DB Treatment and Follow-up phases) will be up to 87 days (up to 30 days for Screening, 43 days for the DB Treatment Phase, and up to 14 days for the Follow-up Phase).

EFFICACY EVALUATIONS

The efficacy of the study intervention will be evaluated using the MADRS (SIGMA), Snaith-Hamilton Pleasure Scale (SHAPS), Dimensional Anhedonia Rating Scale (DARS), Clinical Global Impression-Severity (CGI-S) (depression), PHQ-9, Patient Global Impression of Severity (PGI-S) (depression), PGI-S (anhedonia), Patient Global Impression of Change (PGI-C) (anhedonia), Quality of Life in Depression Scale (QLDS), PROMIS Short Form v2.0 - Ability to Participate in Social Roles and Activities - 8a (PROMIS-APS 8a), Generalized Anxiety Disorder 7-item Scale (GAD-7), and European Quality of Life, 5 Dimension, 5-Level questionnaire (EQ-5D-5L).

PHARMACOKINETIC EVALUATIONS

Sparse blood samples will be collected for measurement of plasma concentrations of aticaprant and any relevant metabolite(s), if warranted, as indicated in the SoA.

SAFETY EVALUATIONS

Safety evaluations during the DB Treatment Phase will include collection of AEs and concomitant medications, as well as assessment with physical examination including a brief neurologic examination, body weight, BMI, vital signs, 12-lead ECG, urine drug test, alcohol breath test, and clinical laboratory tests (hematology, serum chemistry panel, lipid panel, hemoglobin A1c [HbA1c], thyroid-stimulating hormone [TSH], free thyroxine [FT_4], and urinalysis). Serum or urine pregnancy tests will be performed for female participants of childbearing potential. Additional serum and urine pregnancy tests and drug and

[a] The study may enroll more than approximately 538 participants to ensure that 324 adult participants with MDD ANH+ are enrolled. Once the required number of 324 adult participants with MDD ANH+ are enrolled, recruitment of adult MDD ANH- and/or elderly participants may stop if it takes considerably longer to achieve the planned number of participants.

alcohol tests may be conducted as needed per the investigator's judgment. Menstrual cycles will be tracked during the study in female participants who are still having their menses, using a participant diary and participant's verbal report. In addition, emergence of suicidal ideation will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), potential withdrawal effects will be assessed by the clinician using the PWC-20, and sexual functioning will be assessed using the Arizona Sexual Experiences Scale (ASEX).

STATISTICAL METHODS

Sample Size Calculation

Approximately 538 participants, including adults and elderly will be enrolled in this study.

Participants entering the DB Treatment Phase will be randomized in a 1:1 ratio to receive adjunctive aticaprant 10 mg or adjunctive placebo. Across the 2 treatment groups, a minimum of 324 adult participants with MDD ANH+ and approximately 106 adult participants with MDD ANH- will be enrolled. Assuming an effect size of 0.4 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 90% power for the comparison between aticaprant 10 mg and 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 0.45 (mean difference between treatment groups of -4.1 and a pooled standard deviation of 8.98) for the change from baseline to Day 43 in MADRS total score for the relevant study population, and clinical judgment. Given that 67953964MDD2001 was a Phase 2 study, the sample size for the primary efficacy analysis for this Phase 3 study was determined using a smaller effect size of 0.4 to allow for greater variability that can be expected for a global study that is larger in scope.

It is expected that approximately 108 elderly participants (65 years to 74 years of age, inclusive) will be enrolled 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 will be described in the respective country/territory-specific amendments to the protocol.

General Considerations

Data from China and Japan (if participating) will be combined with the global data for local registration in the respective countries/territories. Details about the analysis will be described in a country/territory-specific amendments to the global protocol.

Efficacy Analyses

The primary analysis set is the full analysis set (FAS_ANH+) which is defined as all randomized adult participants with MDD ANH+ who take at least 1 dose of study intervention.

Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in MADRS total score at Day 43 in the FAS_ANH+ analysis set.

***Primary Estimand*:** This estimand is defined to address the primary objective when the study intervention is taken as directed. This estimand has the following 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 participants (18 to 64 years of age, inclusive) with MDD ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI, as reflected by the inclusion/exclusion criteria.

Endpoint: Change in MADRS total score from baseline to Day 43.

Intercurrent events: The following intercurrent events will be managed using a hypothetical strategy (ie, as if the intercurrent event did not occur):

- Discontinuation of study intervention only,
- Discontinuation of both study intervention and current antidepressant,
- Switch of study intervention only (ie, initiation of another antidepressant after discontinuation of study intervention),
- Switch of current antidepressant therapy only,
- Switch of study intervention and current antidepressant therapy.

Summary measure: difference in treatment means.

Primary analysis: Change from baseline in MADRS total score will be analyzed by a Mixed-Effect Model for Repeated Measures (MMRM) based on observed case. 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 MADRS total score as a covariate. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, 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. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. Comparison between aticaprant 10 mg and placebo at Day 43 will be performed using the appropriate contrast. Difference in least square means and 2-sided 95% confidence intervals (CI) will be presented.

Sensitivity analysis: Delta adjustment tipping point will be conducted as a sensitivity analysis.

Any supplementary estimands that are identified will be described in the statistical analysis plan (SAP).

Key Secondary Efficacy Endpoint

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

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

Testing Procedure for Primary and Key Secondary Endpoints

A fixed sequence testing procedure will be applied to control the family-wise error rate (FWER) at 2-sided 0.05 level accounting for multiplicity due to the primary (MADRS total score) and the key secondary efficacy endpoint (DARS total score). The testing procedure will first test the primary endpoint at 2-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.

Safety Analyses

Safety analyses will be based on the safety analysis set, which consists of all randomized participants (adults and elderly) who take at least 1 dose of study intervention.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent AEs, ie, AEs with onset during the DB Treatment Phase, or AEs that are a consequence of a pre-existing condition that has worsened since baseline, will be included in the analysis. For each treatment-emergent AE, and AESI, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study intervention. Serious adverse events will be summarized separately.

The effects on ECG measurements (heart rate, PR interval, QT interval, and QTc interval) will be evaluated using descriptive statistics and frequency tabulations. QTc intervals will be calculated using the Bazett and Fridericia correction methods, and descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval higher than pre-specified levels will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

Laboratory data will be summarized by type of laboratory test and study intervention. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. The proportion of participants with markedly abnormal results will be presented for each analyte and study intervention group.

Descriptive statistics of pulse, sitting blood pressure (systolic and diastolic), body temperature for observed values will be provided and changes from baseline, will be summarized at each scheduled time point by study intervention group. Changes in body weight and BMI will be summarized descriptively.

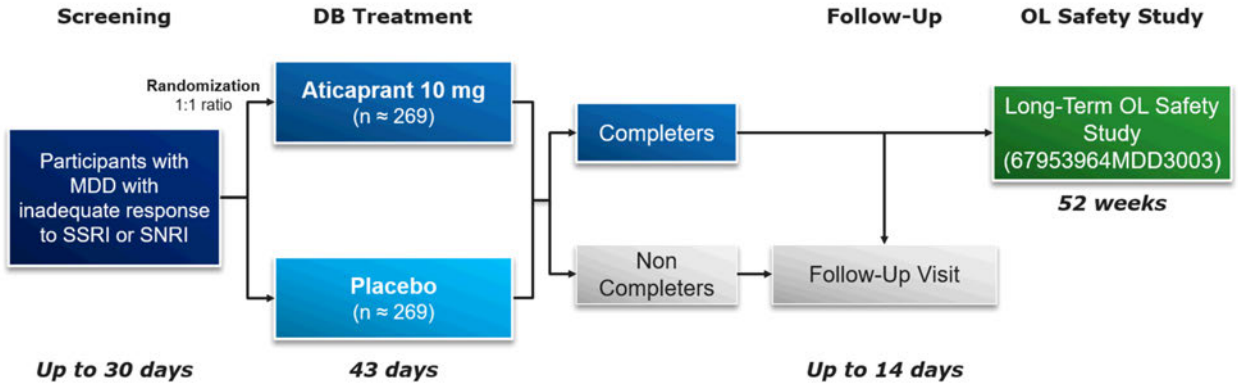
Results from the ASEX, C-SSRS, and PWC-20 will be tabulated by study intervention group.

Interim Analysis

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.

1.2. Schema

Figure 1: Schematic Overview of the Study



Approximately 538 participants (430 adult and 108 elderly) will be enrolled. 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 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 will be described in the respective country/territory-specific amendments to the protocol.

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.

1.3. Schedule of Activities (SoA)

Schedule of Activities during the Screening, Double-blind Treatment, and Follow-up Phase

Phase	Screening[a]		Double-blind Treatment							Follow-up
Visit number	1.1	1.2[b]	2.1 (Baseline)	2.2	2.3	2.4	2.5	2.6	2.7[c] (EOT/EW)	3.1
Study Day	-30 to -2		1	8	15	22	29	36	43	7-14 days after Visit 2.7 (EOT/EW)
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	RC	C	RC	C	RC	C	C
Visit window (days)				±2	±3	±2	±3	±2	±3	
Study Procedure										
Screening/Administrative										
Informed consent (ICF)[d]	X									
ICF for optional genetic research samples[d]	X									
ICF for optional substudies[d]	X									
Medical History, psychiatric history, demographics	X									
Employment status	X								X	
Inclusion/exclusion criteria[e]	X		X[w]							
HDRS-17[f] (Independent Remote Rater), audio teleconferencing	X[f]	X[f]								
SCID-CT	X									
MGH ATRQ[g]	X									
SIQA	X									
MMSE	X[h]									
Pre-study therapy	X									
Preplanned surgery/procedure(s)	X									
Serum pregnancy test[i]	X									
Urine pregnancy test[i]			X[w]		X		X		X	
Height	X									
Weight	X								X	
Study Intervention Administration										
Randomization			X							
Dispense study intervention			X		X		X			
Oral Dose Study intervention[j]			Day 1 until and including Day 42							

Phase	**Screening**[a]		**Double-blind Treatment**							**Follow-up**
Visit number	1.1	1.2[b]	2.1 (Baseline)	2.2	2.3	2.4	2.5	2.6	2.7[c] (EOT/EW)	3.1
Study Day	-30 to -2		1	8	15	22	29	36	43	7-14 days after Visit 2.7 (EOT/EW)
Clinic Visit (**C**) or Remote Contact (**RC**)	**C**	**C or RC**	**C**	**RC**	**C**	**RC**	**C**	**RC**	**C**	**C**
Visit window (days)				±2	±3	±2	±3	±2	±3	
Study Procedure										
Dispense/review study intervention diary[k]			X		X		X		X	
Return/Drug Accountability					X		X		X	
Efficacy Assessments[l]										
MADRS (Site Rater), video teleconferencing			X[w]		X		X		X	X
SHAPS	X		X[w]		X		X		X	X
DARS			X		X		X		X	X
CGI-S			X[w]		X		X		X	X
PGI-S anhedonia			X		X		X		X	X
PHQ-9			X		X		X		X	X
PGI-S depression			X		X		X		X	X
PROMIS-APS 8a[m]			X		X		X		X	X
GAD-7			X						X	
EQ-5D-5L			X		X		X		X	X
QLDS			X				X		X	
PGI-C anhedonia									X	
Safety Assessments										
Physical examination	X		X[w]						X	X
Vital signs	X		X[w]		X		X		X	X
12-lead ECG[n]	X		X[w]				X		X	
ASEX			X				X		X	
C-SSRS: Screening/Baseline version	X									
C-SSRS: Since last visit version		X	X[w]	X	X	X	X	X	X	X
PWC-20									X	X
Clinical Laboratory Tests										
Hematology, Chemistry	X		X[w]						X	
Lipid panel (fasting)		X								
Urinalysis	X		X[w]						X	

Phase	Screening[a]		Double-blind Treatment							Follow-up
Visit number	1.1	1.2[b]	2.1 (Baseline)	2.2	2.3	2.4	2.5	2.6	2.7[c] (EOT/EW)	3.1
Study Day	-30 to -2		1	8	15	22	29	36	43	7-14 days after Visit 2.7 (EOT/EW)
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	RC	C	RC	C	RC	C	C
Visit window (days)				±2	±3	±2	±3	±2	±3	
Study Procedure										
TSH/FT_4; HbA1c	X									
Alcohol breath test	X		X[w]							
Evaluation of current antidepressant compliance[o]	X		X[w]				X		X	
Drug screen (urine)	X		X[w]		X		X		X	
Clinical Pharmacology Assessments										
Blood sample collection[p]			X[q,w]		X[q]		X[q]		X[q]	
Biomarkers Assessments										
Morning blood sample collection[r]			X[w]				X		X	
Menstrual cycle tracking (start date of last menstrual period prior to study visit)[s]	X		X		X		X		X	
Pharmacogenomics and Epigenetic (DNA, RNA) Assessments										
Blood sample collection			X[t,w]						X[t,u]	
Digital Health										
Reward Learning Task[v]			X						X	
Ongoing Review										
Diary for current antidepressant compliance (Dispense/Review)	X		X[w]		X		X		X	
Concomitant therapy	← Continuous →									
Adverse events	← Continuous →									

Abbreviations: ASEX = Arizona Sexual Experiences Scale; C= Clinic Visit; CGI-S = Clinical Global Impression-Severity; C-SSRS = Columbia Suicide Severity Rating Scale; DARS = Dimensional Anhedonia Rating Scale; DB = Double-blind; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOT = End of Treatment; EQ-5D-5L = European Quality of Life, 5 Dimension, 5-Level questionnaire; EW = Early Withdrawal; FT_4 = free thyroxine; FU = Follow-up; GAD-7 = Generalized Anxiety Disorder 7-item Scale; HbA1c test = glycated hemoglobin test; HDRS-17 = 17-item Hamilton Depression Rating Scale; MADRS = Montgomery Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; MMSE = Mini Mental State Examination; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Severity; PHQ-9 = Patient Health Questionnaire, 9-item; PROMIS-APS 8a = Patient-Reported Outcomes Measurement Information System Short Form v2.0 - Ability to Participate in Social Roles and Activities - 8a; PWC-20: Physician Withdrawal Checklist, 20-item; QLDS = Quality of Life in Depression Scale; RC = Remote Contact; RLT = Reward Learning Task; SCID-CT =

Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version; SHAPS = Snaith-Hamilton Pleasure Scale; SIQA = Site Independent Qualification Assessment; TSH = thyroid-stimulating hormone.

Note:

On Clinic (C) Visit days, time 0 is defined as the time of the study intervention intake. Therefore, post-dose time points are referenced from this.
During the site visits, when blood and urine is collected in a fasted condition, it is recommended that procedures should be performed in the following sequence: Blood and urine collection (when in fasted condition), dosing, breakfast, PRO, interview with site-based rater (MADRS [SIGMA version] via videoconference, if not completed before the actual visit; CGI-S), C-SSRS, and safety assessments. Blood collections for PK and PD assessments should be kept as close to the specified time as possible. Of note, at Visit 2.1 (Day 1), PROs, MADRS, CGI-S, and C-SSRS must be completed prior to randomization and dosing.

Footnotes:

a. All screening assessments performed at Visits 1.1 and 1.2 may be conducted on days differing from the actual dates of Visits 1.1 and 1.2. All screening assessments must be performed early enough in order to obtain the results and confirm the eligibility prior to randomization.
b. An optional period is foreseen in the duration of the Screening Phase to taper and discontinue prohibited therapies before baseline. Tapering and discontinuation of therapies should be based on the local prescribing information or clinical judgment of the therapy by the investigator or treating physician. Tapering and discontinuation of prohibited therapies should be initiated after completion of the second HDRS-17 (Visit 1.2) assessment and the SIQA and confirmation these were passed. Participants who do not require a taper and are thus eligible to immediately proceed to the DB Treatment Phase can have their Baseline (ie, Visit 2.1) on the next day following Visit 1.2 provided eligibility is confirmed.
c. If a participant prematurely discontinues from study intervention before the end of the DB Treatment Phase (ie, before completing Visit 2.7) for reasons other than withdrawal of consent, an EOT/EW Visit (ie, Visit 2.7) should be conducted preferably the day after the last dose of study intervention, followed by the Follow-up Phase. If Visit 2.7 is conducted on the same day as a scheduled visit, duplicate assessments are not required.
d. The ICF must be signed before the first study-related activity. Rescreened participants will be assigned new participant numbers, will need to sign a new ICF and restart a new Screening Phase.
e. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Section 10.3. Verify inclusion/exclusion criteria before randomization of each participant.
f. HDRS-17 will be performed by independent remote raters via telephone. The first remote interview will be scheduled as soon as possible after Visit 1.1 and to occur within the first week of the Screening Phase. The second interview should occur at least 1 week (7 days) after the first interview.
g. Two different versions of the MGH ATRQ scale will be used based on age (for participants 18 to 64 years of age, inclusive and for participants 65 to 74 years of age, inclusive).
h. The MMSE screening assessment is to be performed only in participants of 65 to 74 years of age, inclusive.
i. Applicable to female participants of childbearing potential.
j. The first administration of study intervention on Day 1 (Visit 2.1) will occur on-site. At home: study intervention should be taken around the same time and preferably in the morning. At all subsequent clinic visits: study intervention will be administered on-site using dose from the blisters dispensed at that visit and self-administration should be witnessed by the responsible site staff personnel. The exact date and time when the study intervention is administered on-site and the time of the dose on the previous day is required for all visits with PK sampling.
k. Dispense the study intervention diary at Visit 2.1 and review it at all clinical visits (C).
l. All PRO assessments should be conducted in the order listed in the above SoA table. The following PRO assessments will be collected electronically in a 1 to 2-day window prior to the clinic visit: PROMIS-APS 8a, GAD-7, EQ-5D-5L, and QLDS. If a participant does not complete the PRO assessments ahead of the clinic visit, the PROs will be collected at the clinic visit.

m. For participants that require translation of the PROMIS-APS 8a into their local language, the collection of the PROMIS-APS 8a is optional until the final, approved translation is available.
n. At Visits 2.1 (Study Day 1) and 2.5 (Study Day 29), 12-lead ECG will be performed pre-dose and post-dose (ie, 1 to 4 hours after dosing). At Visit 2.7 (EOT/EW), a 12-lead ECG will be performed. During screening or at Visit 2.1 (Day 1), if QTcF is prolonged based on-site evaluated ECG, a total of three 12-lead ECGs should be obtained at least 4 minutes apart. The average QTcF of the three 12-lead ECGs will then be used to determine participant's eligibility. During the DB Treatment Phase, if a clinically significant finding is identified in QTcF, the average QTcF of 3 12-lead ECGs, recorded 4 minutes apart, will be used to assess QTc stopping criteria.
o. During the Screening Phase, compliance to the current antidepressant treatment must be confirmed by documented records (eg, medical/pharmacy/prescription record, a letter from a treating physician, etc). During the DB Treatment Phase, the compliance to the SSRI or SNRI (the one that is continued in this phase) will be assessed by documented records (medical/pharmacy/prescription records, pill counts etc). In absence of other options to assess compliance, blood or urine levels can be used by the site to evaluate the adherence to the antidepressant treatment.
p. If blood sampling or vital sign measurement is scheduled for the same time point as 12-lead ECG recording, the procedures are recommended to be performed in the following order: 12-lead ECG, vital signs, blood draw.
q. At Visits 2.1 (Study Day 1) and 2.5 (Study Day 29), PK samples will be collected from all participants pre-dose and at around peak (1 to 4 hours after dosing). At Visit 2.3 (Study Day 15), only a pre-dose PK sample will be collected. At Visit 2.7 (EOT/EW), a PK sample will be collected. In addition, an optional unscheduled blood sample may be collected throughout the DB Treatment Phase visits for determination of plasma concentrations of aticaprant in participants who discontinue study intervention for an AESI or SAE which is related to AESI. This blood sample should be collected as close as to the AESI or AESI related SAE occurrence, but preferably within 72 hours of the last study intervention administration. This sample is not collected in case of discontinuation due to AE, but only for AESI or AESI related SAE.
r. Biomarker samples will be collected under fasting conditions and prior to study intervention administration.
s. Only applicable to female participants with a menstrual cycle.
t. Blood samples will be collected only from participants who have consented to provide optional DNA and RNA samples for research. Samples will be collected at the same time as the protein blood biomarker samples.
u. For RNA, an optional second sample may be collected at the end of the DB Treatment Phase (Visit 2.7).
v. The Reward Learning Task will only be performed in English-speaking countries/territories.
w. Study procedure or assessment must be performed before randomization.

2. INTRODUCTION

An increased understanding of the neurobiology of mood disorders allows for targeted research and focus on specific brain circuits implicated in mood. This provides an opportunity for developing improved treatments of mood disorders which are informed by the underlying neurobiology (Machado-Vieira 2011). Existing evidence implicates the dynorphin opioid neuropeptide system (Chavkin 1982) in the regulation of mood (Chartoff 2009; Pecina 2019; Schwarzer 2009; Shirayama 2004). Kappa opioid receptor (KOR) activation by the endogenous dynorphin induces stress and depressive symptoms in humans and animals (Bruchas 2010; Escobar 2020) and downstream results in decreased dopaminergic function in different brain areas (Margolis 2006; Tejeda 2017). It is hypothesized that selective modulation of the KOR would result in improvement of residual symptoms of depression, including behaviors involving anhedonia, by restoring normal dopamine transmission in the brain's reward/motivation circuitry (Carlezon 2009b; Carlezon 2016; Krystal 2020; Rorick-Kehn 2014). Preclinical evidence supports the therapeutic potential of KOR antagonism for the treatment of anhedonia, depression, and anxiety (Beardsley 2005; Carr 2010; Lutz 2014; Mague 2003; Rorick-Kehn 2014; Walker 2008). Based on an emerging body of scientific evidence, selective KOR antagonism may provide therapeutic benefit in the treatment of major depressive disorder (MDD).

Aticaprant (JNJ-67953964) is a once daily, highly selective KOR antagonist, with demonstrated selectivity over mu opioid receptor (MOR) and delta opioid receptor (DOR) (Carlezon 2009a; Naganawa 2016), that is being developed for adjunctive treatment of MDD in patients with moderate-to-severe anhedonia (MDD ANH+).

Aticaprant has shown antidepressant-like effects in preclinical studies and had synergistic effects when administered with a subactive dose of imipramine. Clinical data from multiple Phase 1 and results from 2 well-controlled Phase 2 studies provide complimentary positive evidence for efficacy of aticaprant in patients with major depression with anhedonia (Krystal 2020). Study 67953964MDD2001 provides proof of efficacy showing that after 6 weeks of treatment MDD participants randomized to aticaprant added to ongoing antidepressant achieved statistically significant and clinically meaningful reduction in overall depression severity on the Montgomery-Åsberg Depression Rating Scale (MADRS, primary endpoint) compared with those who continued on the current antidepressant plus placebo. Furthermore, MDD participants with a high level of anhedonia at entry (measured by higher total Snaith-Hamilton Pleasure Scale [SHAPS] score) when treated with 10 mg/day aticaprant added to a selective serotonin reuptake inhibitor (SSRI/)/serotonin-norepinephrine reuptake inhibitor (SNRI) showed greater improvement in overall depression severity. The clinical outcomes in Study 67953964MDD2001 are complemented by the results from an investigator-initiated study (IIS) FAST-MAS, which showed that KOR antagonism by aticaprant has a coherent effect on measures of anhedonia across units of analysis on brain activity, behavior, and self-report, thereby establishing proof of mechanism that by blocking the KOR, aticaprant can modulate neuronal circuits relevant to reward and hedonic response. Overall, aticaprant has been safe and well tolerated in patients.

For the most comprehensive nonclinical and clinical information regarding aticaprant, refer to the latest version of the Investigator's Brochure (IB) and Addenda.

The term “study intervention” throughout the protocol, refers to study intervention as defined in Section 6.1.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

2.1. Study Rationale

Depression is a common and serious psychiatric disorder affecting approximately 280 million individuals worldwide (according to the World Health Organization [WHO] Fact Sheet 2021 [WHO 2021]). Depression is a leading cause of disability worldwide and is associated with elevated mortality and suicide risk (WHO 2021; Walker 2015). A noticeable increase in the global burden of depressive disorders has been observed due to the COVID-19 pandemic with an estimated additional 53.2 million cases of MDD globally (COVID-19 Mental Disorders Collaborators 2021; Ettman 2020).

An inadequate response to first-line standard-of-care antidepressant treatment for MDD remains a significant problem resulting in persistent impairment and high utilization of health care resources (Kennedy 2004). While switching antidepressants and using adjunctive treatments may improve response, almost 40% of patients remain symptomatic and fail to achieve full remission (Rush 2006). Symptoms such as loss of interest/pleasure (anhedonia), insomnia, fatigue, have been reported to persist in patients treated with current antidepressants (Spijker 2001; Taylor 2010; Wardenaar 2012).

Persistence of anhedonia has been linked to poorer outcomes in patients with MDD and has been associated with increased overall severity of depressive symptoms (Gong 2017); a chronic course of depression over a 10-year period (Moos 1999); longer time to remission (McMakin 2012; Spijker 2001; Uher 2012) and functional and quality-of-life impairment (McMakin 2012; Vrieze 2013). MDD patients with anhedonia have higher incidence of acute cardiac events and mortality (Davidson 2010).

Opioid receptors are widely found throughout the central nervous system and are believed to be involved in several important functions. Three distinct subtypes of opioid receptors have been identified and characterized: mu (MOR), delta (DOR) and kappa (KOR). The KORs and the endogenous ligand dynorphin are highly expressed within the prefrontal cortico-striatal loop, which mediates reward and affective states (Carlezon 2009b; Naganawa 2014; Naganawa 2016). As such the kappa opioid system is one of the most preponderant systems controlling dopamine transmission in the reward/motivation circuit. Emerging evidence has implicated the role of overactivation of the KOR system in regulation of mood symptoms (Gray 1999), especially anhedonia (Williams 2018). Selective blockade of the KOR by KOR antagonists like aticaprant has shown to modulate neuronal circuits relevant to reward and hedonic response (Krystal 2020;

Pizzagalli 2020) and by restoring the dopamine release homeostasis leads to improvement in depressive symptoms (Carlezon 2009a; Krystal 2020).

The therapeutic mechanism of action (Carlezon 2016; Urbano 2014) and evidence gathered so far support considerations for added benefit to the standard-of-care SSRI/SNRI in improving depressive symptoms based on the underlying neurobiology ie, by modulation neuronal circuits relevant to reward and hedonic capacity and restoring dopamine release homeostasis.

The proposed study is a randomized, double-blind, placebo-controlled, 6-week study to assess the efficacy, safety, and tolerability of aticaprant as adjunctive therapy to SSRI/SNRI in adult (18 to 64 years, inclusive) participants with MDD ANH+ who have had an inadequate response to an SSRI/SNRI in the current depressive episode.

2.2. Background

Nonclinical Studies

Nonclinical Pharmacology

Kappa Opioid Receptor Studies: Aticaprant (JNJ-67953964) is a potent, high-affinity antagonist (inhibition constant [Ki]=0.807 nM) for KORs, with demonstrated selectivity over MORs and DORs, as assessed by in vitro binding and functional assays. In vivo, aticaprant produced a dose-dependent increase in KOR occupancy in both rat and mouse, with a calculated dose that produces 50% of maximum effect (ED_{50}) of 0.3 mg/kg in the rat and 90% occupancy at 10 mg/kg in both species. At pharmacologic doses, aticaprant showed no appreciable occupancy at MORs and DORs, but dose-dependent pharmacodynamic effects were observed at supratherapeutic doses. In various pharmacology assays, including reversal of kappa- and mu-agonist-induced analgesia effects and prepulse inhibition, aticaprant produced potent and selective blockade of kappa, but not mu, agonist-mediated effects. In vitro assessment of aticaprant metabolites at 1 mM concentrations, showed formation of a pharmacologically active metabolite (M3, JNJ-78430885, originating from methyl oxidation on the dimethylphenyl to an acid) that inhibited MOR, DOR, and KOR binding (86%, 62%, and 99%, respectively). Metabolite M3 was 5-fold more potent as a KOR antagonist than JNJ-67953964 (concentration producing 50% of maximal inhibition [IC_{50}] of 1 vs 5-7 nM). However, KOR occupancy mediated by M3 in rat brain was much lower than with JNJ-67953964, indicating that M3 does not contribute to the pharmacological activity in vivo.

Aticaprant (1 μM) has no appreciable affinity at several non-opioid cell surface receptor targets, including monoaminergic, muscarinic, cholinergic, and adrenergic receptors, as well as the central benzodiazepine binding site, ion channels, or transporters.

In vivo studies conducted in mice have demonstrated the therapeutic potential of the KOR antagonist aticaprant in blocking signs of (i) spontaneous nicotine withdrawal and (ii) nicotine withdrawal induced pharmacologically with the nicotine antagonist mecamylamine. JNJ67953964 also reduced high alcohol intake behavior in alcohol-preferring rats with a chronic alcohol drinking history, without affecting food or water intake. Aticaprant showed antidepressant-like effects in mice and had synergistic effects when administered with a subactive dose of imipramine.

Antidepressant-like effects of aticaprant were demonstrated in the mouse Forced Swim test. This is a validated animal model of clinical MDD that demonstrates predictive validity for all known classes of effective antidepressants, with antidepressant-like activity indicated by reductions in immobility. Aticaprant reduced the time spent immobile in a dose-dependent manner, with 10 mg/kg achieving efficacy comparable to that of the tricyclic antidepressant imipramine (15 mg/kg intraperitoneal) (refer to the IB).

Aticaprant had no effect on dopamine release in the nucleus accumbens suggesting low potential for abuse liability.

Safety Pharmacology

Aticaprant was evaluated in a variety of in vitro and in vivo models for effects on the cardiovascular, respiratory and central nervous systems, and did not show any potential for adverse effects. No noticeable changes in hemodynamic and electrocardiographic parameters (quantitative and qualitative; rhythm/waveforms), and on body temperature up to 1,000 mg/kg were observed. No treatment-related effects on QT or QT intervals by Fridericia's method (QTcF) intervals were observed in repeat-dose toxicity studies in dogs up to ≥1,000 mg/kg/day. Aticaprant showed no major effect on neurobehavioral functions in rats. Aticaprant does not disrupt motor functioning of attentional processes. No relevant adverse effects on the rat central or peripheral nervous systems up to 100 mg/kg/day. Single doses of 100, 300, and 800 mg/kg were associated with calmer animals in their home cage between 1 hour and up to 24 hours after dosing (duration related to dose). Aticaprant up to 800 mg/kg did not exert any noticeable effects on the respiratory rate, tidal volume or minute volume in rats from 30 to 360 minutes (0.5 to 6 hours) after dosing (refer to the IB).

Toxicology

The toxicity profile of aticaprant has been extensively evaluated and characterized in both in vitro and in vivo single and repeat-dose, reproductive, genotoxicity, and safety pharmacology, studies conducted in various species (rat, mouse, rabbit, dog, and monkey).

In nonclinical safety pharmacology studies with aticaprant in rats, there were no effects on the central and peripheral nervous systems or the respiratory function up to 800 mg/kg. In dogs, a cardiovascular safety study of single doses up to 1,000 mg/kg, found no statistically significant changes in blood pressure, heart rate, or QT and QTcF intervals. Repeat-dose studies of up to 3 and 9 months in rats and dogs, up to 2 weeks in mice, and up to 7 days in monkeys have been completed. A single dose of 2,000 mg/kg/day in mice, and repeated doses of ≥800 mg/kg/day in rats, and ≥200 mg/kg/day in rabbits exceeded the maximum tolerated dose resulting in adverse clinical signs, decreased food consumption and body weight, and mortality/euthanasia. Target organs were the central nervous system (convulsions in mice, rats, rabbits) and the gastrointestinal tract (in rodents and rabbits).

Convulsions were noted after 1 or 2 doses of aticaprant at 2,000 mg/kg/day (mice), 1,500 mg/kg/day (rats), or 1,000 mg/kg/day (rabbits). The animal-to-human exposure multiples at

the no effect level for convulsions were at least 148-fold based on C_{max} in the most sensitive species (rabbit) and steady-state C_{max} at a 10-mg human dose.

Gastric lesions, including gastric mucosal alterations, decreased parietal cells and gastric mucous cells hypertrophy/hyperplasia and macroscopic stomach lesions associated with microscopic damage to parietal cells, were noted in rodents (mice, rats) and rabbits, but not in dogs or monkeys. The no-observed-adverse-effect level (NOAEL) for gastrointestinal (GI) lesions in the 3-month toxicity study in rats was 15 mg/kg/day in male rats and 75 mg/kg/day in female rats. The dose level of 15 mg/kg/day and 75 mg/kg/day in male and female rats, respectively, corresponded to animal-to-human exposure multiples (AUC-based) of 1-fold and 15-fold in male and female rats, respectively, based on a 10 mg clinical dose.

Overall, the gastric changes were minimal to moderate in severity, not life-threatening, and partially reversible over a 1-month recovery period following the 6-month study. A NOAEL of 15 mg/kg/day and 75 mg/kg/day was established in male and female rats, respectively. Adaptive non-adverse minimal to mild findings were seen also in the liver, adrenal gland, and thyroid gland of rats. These changes were not observed in clinical studies conducted to date.

No effects on fertility or embryofetal development were observed up to 60 mg/kg/day in rabbits and 400 mg/kg/day or 500 mg/kg/day in female and male rats, respectively.

Aticaprant was not phototoxic and not genotoxic in a standard battery of nonclinical tests. Based on the result of a local lymph node assay, aticaprant is regarded as a skin sensitizer. A 2-year carcinogenicity study by oral (gavage) administration in rats is ongoing and a 6-month transgenic mice study is planned.

In general, data from these studies demonstrated an adequate characterization of the toxicology profile, showed dose dependency of the effects, and partial to full reversibility of all toxic effects.

Pharmacokinetic Profile in Animals

Aticaprant is orally bioavailable and brain penetrant. Aticaprant is highly plasma protein (>99%) bound in human, dog, rat, and mouse. Metabolism is primarily through CYP3A4 and CYP2C9. Based on the available in vitro data, the potential of aticaprant to inhibit enzymes or transporters is evaluated to be low. The circulating metabolites of aticaprant are considered qualitatively comparable between the species used in toxicology studies and humans, based on a (preliminary) identification of circulating metabolites in human plasma.

Clinical Studies

Human Pharmacokinetics

Single-dose administration (Study I2Z-MC-LAFA [Lowe 2014]) of aticaprant as an oral capsule to healthy participants resulted in rapid absorption with peak plasma concentrations typically occurring at 1.5 to 4 hours post-dose, proportional increases in exposure with increasing dose (ranging from 2 to 60 mg), and a concentration-time profile indicative of biexponential disposition.

After the 10-mg dose, the geometric mean (present of coefficient of variation percentage [CV%]) for apparent plasma clearance was 28.7 L/hr (36%), apparent volume of distribution at steady state was 1,160 L (25%), and half-life ($t_{1/2}$) was 38.5 hours (22%). The mean $t_{1/2}$ of aticaprant ranged from 21.3 to 38.5 hours and appeared to be independent of dose in the single ascending dose study.

Administration of multiple doses of aticaprant (2, 10 or 35 mg daily for 14 days) resulted in an average accumulation ratio across dose groups of 1.8 (range: 1.8 to 1.9), with dose proportional increases in exposure levels and steady-state achieved after 6 to 8 days of once daily dosage. In this study, the steady-state PK of aticaprant was not affected by the coadministration of a single dose of ethanol. Similarly, the single dose PK of ethanol was not affected by coadministration of multiple doses of 10 mg aticaprant.

In the GI safety study (67953964EDI1001), PK exposures on Day 14 and Day 28 were similar and higher compared with Day 1 exposures consistent with expected accumulation upon multiple dosing and drug's half-life. The trough plasma concentrations achieved on Days 14 and 28 were at steady state and similar.

In Study 67953964EDI1003 evaluating the food effect at a single dose of 10 mg of aticaprant, high-fat breakfast given approximately 30 minutes prior to study intervention has delayed t_{max}, increased bioavailability with 1.5-fold higher exposure in AUC. In the same study, a drug-drug interaction evaluation with a repeated dose of itraconazole (a strong CYP3A4 inhibitor) increased the exposure of aticaprant by 1.3-fold (C_{max}) and 2-fold (AUC).

In Study 67953964EDI1002 evaluating the PK in Asian adult males, the apparent clearance and apparent volume of distribution of aticaprant following a single dose appeared consistent with those observed in single-dose study LAFA (non-Asian population [Lowe 2014]).

The results from relative bioavailability study (67953964MDD1003) have indicated that the 2 tablet formulation concepts tested showed similar in vivo PK performance as active pharmaceutical ingredient (API) in capsule formulation. In addition, PK dose-proportionality was established using 5 and 10 mg tablet strengths. The exposure (AUC) of tablet formulation increased in the presence of high-fat diet by approximately 50% compared to when given in the fasted condition. In CSF penetration assessment part of this study for aticaprant and metabolite M3, CSF levels of aticaprant provide >90% RO with CSF/unbound plasma ratio of ~1 (0.014 ng/mL for >90% RO in rat). CSF levels achieved for M3 are too low to contribute to the pharmacological activity of aticaprant with CSF/plasma unbound ratio of <1 (0.25 ng/mL for 50% RO in rat and 0.359 ng/mL based on binding affinity to human kappa opioid receptors) and is not important.

Based on population PK analysis in non-Asian participants, gender and age were not found to be significant covariates (range: 18 to 64 years) while body weight was found to be a significant covariate from this PK analysis. Based on dose-normalized PK profiles, the PK was comparable between adult and elderly (up to 73 years) participants using API in capsule formulation (67953964MDD1003).

Efficacy Studies

A completed Phase 2a investigator-initiated study (IIS) (FAST-MAS) designed to determine whether KOR antagonism could have effects supportive of therapeutic benefit for anhedonia in patients with mood-anxiety spectrum disorders and anhedonia, revealed a significant Group×Time interaction in reward gain anticipation (p=0.019) (a priori primary outcome) and loss anticipation (p<0.001). In this study, participants with self-reported anhedonia (with a mood or anxiety disorder) were administered monotherapy for a period of 8 weeks: 10-mg aticaprant (n=45) or placebo (n=44). Treatment with aticaprant 10 mg given as a monotherapy, resulted in significantly higher learning rate and a more sustained preference toward the more frequently rewarded stimulus, although reward sensitivity was unaltered compared with placebo. A significant reduction in the severity of anhedonia symptoms was seen on the SHAPS (p=0.0345) with a significant treatment effect on the Temporal Experience of Pleasure Scale consummatory subscale (p<0.02). The results of this study established that KOR antagonism by aticaprant had the hypothesized effect, ie, a coherent effect on measures of anhedonia across units of analysis on brain activity, behavior, and self-report, thereby establishing proof of concept that engaging this target can modulate neuronal circuits relevant to reward and hedonic response (Krystal 2020; Pizzagalli 2020).

The Phase 2 Study 67953964MDD2001 was a randomized, DB, placebo-controlled, parallel-group, multicenter study investigating the efficacy, safety, tolerability, and PK of adjunctive aticaprant in participants with MDD. The objective of this study was to evaluate the efficacy of 10-mg daily aticaprant versus placebo when administered as an adjunctive treatment to participants with MDD who had partially responded to standard-of-care treatment with SSRI/SNRIs. The primary endpoint was reduction of symptoms of depression, as assessed by the change from baseline on the MADRS during a 6-week treatment period. The study included an enrichment design intended to identify possible placebo responders by including a DB placebo run-in period of up to 3 weeks before the treatment period, and 2 weeks of placebo run-out after the 6-week treatment period to explore for indications of worsening or withdrawal. ‘Responders’ during the placebo lead-in period were those participants with ≥30% improvement on the MADRS total score over 3 weeks. The ‘enriched’ analysis set (enriched intent-to-treat [eITT] population) included participants with <30% improvement during the placebo run-in and was considered as primary analysis set, while the ‘full’ analysis set included all participants (full intent-to-treat [fITT] population) regardless of change in the MADRS during the placebo run-in. The study included 169 participants in the safety population, of which 166 participants were included in the fITT population. Of these 166 fITT participants, 121 participants had not responded to placebo during the lead-in period, and thus represented the eITT population; the remaining 45 participants had responded to placebo during the lead-in period and were thus excluded from the eITT population.

The Phase 2 study 67953964MDD2001 showed greater reduction in overall depression severity on the Montgomery-Åsberg Depression Rating Scale (MADRS) in participants with MDD treated with aticaprant added to ongoing antidepressant with partial response, compared with those who continued treatment with just their current antidepressant plus placebo. Participants randomized to aticaprant had a significantly greater reduction in depression severity on the MADRS during the

6-week treatment period- with MADRS (LS) mean difference change from baseline at Treatment Week 6 between aticaprant and placebo being -2.1 with 80% 1-sided CI upper limit of -1.09 (1-sided p=0.044) in the eITT population. In the fITT population, the estimated LS mean difference was of a larger magnitude -3.1 with 80% 1-sided CI upper limit of -2.21; 1-sided p=0.002. In a pre-specified subgroup analysis, the magnitude of the overall antidepressant efficacy was greater in participants with elevated anhedonia compared with those with less severe anhedonia. In a post hoc item-level analysis of the MADRS scale, the subgroup of MDD with elevated anhedonia when treated with aticaprant showed overall better effect on symptoms of dysphoria such as apparent and reported sadness compared with low-to-no anhedonia and in addition, there was improvement in items that reflect the positive affect, namely the anhedonia-specific item inability to feel, and several other items such as pessimistic thoughts, lassitude and concentration difficulties which are related to the hedonic capacity.

Safety Studies

Aticaprant was generally well tolerated in healthy participants after single-dose administration up to 60 mg (Study I2Z-MC--LAFA [Lowe 2014]) or after multiple-dose administration up to 35 mg for 14 days (Study I2Z-MC-LAFB [Lowe 2014]), with no clinically significant AEs, vital signs, 12--lead electrocardiograms (ECGs), or clinical laboratory evaluations reported. No deaths or SAEs were reported in any of these studies. One participant was discontinued due to a mild treatment-related AE of 5-beat ventricular tachycardia.

Safety results from Study 67953964MDD2001 in participants with MDD were consistent with the known safety profile of the drug over a 6-week exposure period. Overall, during the treatment period, 47.1% of participants receiving aticaprant experienced a treatment-emergent adverse event (TEAE), compared with 35.7% of participants receiving placebo. The most common TEAEs during the treatment phase were (aticaprant vs placebo) headache (11.8% vs 7.1% in the placebo group) and diarrhea (8.2% vs 2.4% in the placebo group). TEAEs of special interest in the aticaprant group that were commonly reported were CCI [redacted] CCI [redacted] None of the TEAEs were assessed by the investigator as very likely related to the study intervention.

Similarly, in the FAST-MAS Study, aticaprant was generally well tolerated. No SAEs were reported. Most of the AEs were mild in severity. The AEs of moderate-to-severe severity that showed an incidence >5% (aticaprant vs placebo) included headache (11.1% vs 9.1%), pruritus (11.1% vs 2.3%), anxiety, insomnia, and suicidal ideation (each 6.7% vs 4.5%), diarrhea (6.8% vs 2.2%), and depression and rash (each 6.7% vs 0%).

The gastric findings identified in rodents are considered species-specific as no parietal cell damage or adverse changes in gastric pH were seen in the clinical Phase 1 Study 67953964EDI1001, in which the upper gastrointestinal-related safety and tolerability of aticaprant (25 mg, once daily) was investigated in healthy participants following 4 weeks treatment. Evaluation of the gastric biopsies for microscopic signs of ulcers or erosions produced normal outcome at Day 28 for all participants. Evaluation of changes in pH and biomarkers of gastric mucosal function did not show

treatment differences over the course of the study. Overall, the endoscopic evaluations and biochemical studies did not produce any evidence for an effect of aticaprant on parietal cells.

Furthermore, review of completed Phase 1 and Phase 2 human studies for TEAEs suggestive of abuse potential did not identify AEs indicative of abuse potential.

2.3. Benefit-Risk Assessment

The theoretical and potential risks of exposure to aticaprant based on its mechanism of action are summarized below. More detailed information about the known and expected benefits and risks of aticaprant may be found in the IB.

2.3.1. Benefits for Study Participation

There is evidence to suggest that with its targeted mechanism of action the selective KOR antagonism may result in improvement of symptoms of depression linked to impaired functioning in the reward circuitry (like anhedonia and amotivation) (Borsini 2020) and which are poorly addressed by the current standard-of-care SSRIs/SNRIs, (Calabrese 2014; Craske 2019; Vrieze 2013). Presence and persistence of symptoms like elevated anhedonia predict poor outcome and chronic course of the disease (Moos 1999; Spijker 2001; Uher 2012). Available data from nonclinical and clinical studies (Phase 1 and Phase 2 studies) with aticaprant support the scientific and clinical rationale for the use of selective KOR antagonists in the treatment of depression with moderate-to-severe anhedonia. Data from the Phase 2 study 67953964MDD2001 showed greater reduction in overall depression severity on the MADRS in participants with MDD treated with aticaprant added to ongoing antidepressant with inadequate response, compared with those who continued their current antidepressant plus placebo. The magnitude of the overall antidepressant efficacy was different when examined based on the presence and severity of anhedonia defined using an established self-reported assessment (SHAPS) for severity of anhedonia. When treated with aticaprant, participants with a high level of anhedonia at entry, showed greater improvement of overall depressive symptoms compared with those with a low level of anhedonia. In a post hoc item-level analysis of the MADRS scale, the subgroup of participants with a high level of anhedonia when treated with aticaprant showed overall better effect on symptoms of dysphoria like apparent and reported sadness compared with participants with a low level of anhedonia, and there was improvement in items that reflect the positive affect, namely the anhedonia-specific item inability to feel, and several other items like pessimistic thoughts, lassitude and concentration difficulties, which are related to the hedonic capacity as they reflect on individual's interest, engagement, motivation, and activity. Improvement in MADRS scores of symptoms of depression (eg, sadness, tension, appetite, insomnia, and fatigue) were observed. Furthermore, aticaprant was generally safe and well tolerated. Participants in this study will help in evaluating the use of aticaprant in the treatment of MDD and specifically in MDD with moderate-to-severe anhedonia, and in increasing our understanding of the disease indication. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering from MDD with moderate-to-severe anhedonia and offers potential public health benefits.

Participants may also experience some benefit from the participation in a clinical study irrespective of receiving study intervention, due to regular visits and assessments monitoring their overall health.

2.3.2. Benefit-Risk Assessment for Study Participation

Study 67953964MDD3002 is the second Phase 3 study investigating the therapeutic efficacy of adjunctive aticaprant therapy in participants with MDD with moderate-to-severe anhedonia who have had an inadequate response to standard-of-care antidepressant treatment with an SSRI/SNRI. Therefore, the benefit-risk profile of adjunctive aticaprant therapy in this patient population has not been fully established.

The currently available data (see Section 2.2), and the aticaprant IB support this clinical study that investigates the efficacy, safety and tolerability of aticaprant as adjunctive therapy in adult (18 to 64 years, inclusive) and elderly (65 to 73 years, inclusive) participants with MDD ANH+ who have had an inadequate response to antidepressant therapy with a SSRI/SNRI in the current depressive episode.

Aticaprant was generally well tolerated in healthy participants after single-dose administration up to 60 mg or after multiple-dose administration up to 35 mg for 14 days, with no clinically significant AEs, vital sign measurements, 12-lead ECGs, or clinical laboratory evaluations reported (see Section 2.2).

In this study, 10 mg/day given once daily will be evaluated. The 10 mg/day dose selection is based on the results from the completed Phase 2a Studies FAST-MAS and Study 67953964MDD2001, as well as PK/PD and RO modeling.

The expected exposure in Study 67953964MDD2001 after 10 mg aticaprant once daily is predicted to result in a nearly complete inhibition of KORs at C_{max}. Moreover, the median RO is predicted to be [redacted] % and [redacted] % of the maximum RO at the trough and peak levels, respectively. This relatively modest variation across the interdose interval is expected to achieve [redacted] % kappa RO at the 10 mg/day dose in most participants.

To date, clinical studies have only been conducted with aticaprant dose of 10 mg in younger adults up to 65 years of age. The data from these studies did not yield safety and tolerability effects that might be of concern for older adults (ie, no cardiovascular effects, metabolic effects, or sedation). Considering the PK/PD and observed safety for aticaprant, it is expected that older adults (up to 74 years) may exhibit a similar tolerability and efficacy profile to younger adults.

The scientific and clinical evidence (clinical pharmacology data, receptor occupancy modeling, safety database and efficacy data from Phase 2) supports 10 mg/day as a safe dose that would provide optimal efficacy in adjunctive treatment, where the ultimate goal is to adequately manage the remaining symptoms and undertreatment is not desirable. This short-term Phase 3 study will therefore assess a dosage of 10 mg/day for efficacy as part of the primary analysis.

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with aticaprant are justified by the anticipated benefits that may be afforded to participants; this supports further clinical investigation of adjunctive treatment with aticaprant for MDD in patients with moderate-to-severe anhedonia.

3. 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.
• 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).

Objectives	Endpoints
	• 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 - 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+, adult participants with MDD ANH-, and all MDD participants (adult and elderly participants with MDD ANH+ and MDD ANH-) 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 MDD ANH- and All MDD). • Change from baseline over time in the MADRS-6 score. • 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 MDD ANH- 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 (reduction in DARS total score ≥ meaningful change threshold [or range of thresholds] determined by anchor-

Objectives	Endpoints
	based analyses of blinded interim data, as indicated in Section 9.5).
• 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, 5 Level (EQ5D5L) 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).
Clinical Pharmacology Assessments	
• To assess the PK 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 AEs.	
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, PK, safety, or tolerability of aticaprant.	
• To confirm the diagnostic value of the 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]).	

HYPOTHESIS

The hypothesis for this study is that adjunctive treatment with aticaprant 10 mg is superior to placebo in treating depressive symptoms, as measured by change in MADRS total score from baseline (Day 1, pre-randomization) to Day 43 in adult participants with MDD ANH+ who have had an inadequate response to treatment with an SSRI/SNRI.

4. STUDY DESIGN

4.1. Overall 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 MDD with moderate-to-severe anhedonia (MDD ANH+), adult participants who do not have moderate-to-severe anhedonia (MDD ANH-), and elderly participants (65 to 74 years of age, inclusive) with MDD (ANH+ and ANH-). All participants must have had an inadequate response to an SSRI/SNRI in the current depressive episode.

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

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

- 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.

A target of approximately 538 participants,[a] including adults (18 to 64 years of age, inclusive) and elderly (65 to 74 years of age, inclusive) will be enrolled in this study. Participants entering the DB Treatment Phase will be randomized in a 1:1 ratio to receive adjunctive aticaprant 10 mg or placebo. A minimum of 324 adult participants with MDD ANH+ and approximately 106 adult participants with MDD ANH- will be enrolled. With this sample size, it is estimated that approximately 108 elderly participants with MDD (ANH+ and ANH-) will be randomized. The criteria that define MDD ANH+ will be included in an addendum to the protocol and will be blinded to the study sites.

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 will be described in the respective country/territory-specific amendments to the protocol.

[a] The study may enroll more than approximately 538 participants to ensure that 324 adult participants with MDD ANH+ are enrolled. Once the required number of 324 adult participants with MDD ANH+ are enrolled, recruitment of adult MDD ANH- and elderly participants may stop if it takes considerably longer to achieve the planned number of participants.

The adult MDD ANH+ population randomized to aticaprant 10 mg or placebo, will be included in the primary analysis set. The elderly will be analyzed as an exploratory objective along with all adult participants regardless of anhedonia status.

4.1.1. Study Intervention(s)

Participants will be randomized to receive aticaprant 10 mg or placebo. The study intervention will be administered orally as 2 film-coated tablets to be administered together, once daily, around the same time and preferably in the morning.

Participants will receive either aticaprant (10 mg) or matching placebo administered orally once daily in addition to their current antidepressant (SSRI/SNRI) therapy which will be continued during the entire study.

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 who have completed the DB Treatment Phase (Day 43) 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).

The maximum duration of participation in the study for an individual participant (including Screening, DB Treatment and Follow-up phases) will be up to 87 days (up to 30 days for screening, 43 days for the DB Treatment Phase, and up to 14 days for the Follow-up Phase).

4.1.2. Screening Phase

After providing signed informed consent, all the participants experiencing a major depressive episode will be screened to evaluate their eligibility for study participation. Participants must 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 HDRS-17 total score ≥20 at the first and second screening interviews with no greater than 20% improvement from the first to second independent HDRS-17 assessments at screening.

At the start of screening participants must have had an inadequate response to at least 1 oral antidepressant treatment (SSRI or SNRI), administered at an adequate dose (at or above the minimum therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current depressive episode (see Section 5.1, Inclusion Criterion 5). The current antidepressant cannot be

the first antidepressant treatment for the first lifetime episode of depression. An inadequate response is defined as <50% reduction in depressive symptom severity but with some improvement (>0%; ie, 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. This must apply to the participant's current antidepressant treatment. Medical/pharmacy/prescription records or records of conversation with the treating physician, or other equivalent documents can be used to verify the adequacy of the current antidepressant trial.

To characterize the presence and severity of anhedonia from the participant perspective, SHAPS will be collected at screening and at baseline (Day 1, pre-randomization).

A Site Independent Qualification Assessment (SIQA) will assess the validity of the participants' diagnosis and antidepressant treatment response for inclusion in the study.

All participants will continue their current antidepressant (SSRI/SNRI) therapy during the Screening and DB Treatment Phase. The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. Participants will only continue one of these allowed antidepressants at an adequate and tolerated dose during the study. No changes in background antidepressant or dose are permitted from screening until the end of the study treatment phase (see Section 6.8.1 for details). The sponsor will not supply these antidepressant medications.

Prohibited medications will be stopped prior to the start of the DB Treatment Phase. Tapering or time of discontinuation of a prohibited medication prior to the start of the DB Treatment Phase should be based on drug's half-lives, potential drug-drug interactions, local prescribing information or clinical judgment (see Section 6.8.2 for details). Tapering and discontinuation of prohibited therapies should be initiated after completion of the second HDRS-17 (Visit 1.2, see Section 1.3) assessment and the SIQA and confirmation these are passed. Eligible participants who do not require a tapered discontinuation of their prohibited treatment(s) can immediately proceed into the DB Treatment Phase.

If needed (eg, a longer tapering required for prohibited therapies or other circumstances) the screening period may be extended for up to 3 weeks after consultation with sponsor's medical monitor or designee.

Of note, participants taking benzodiazepines (at dosages equal to or less than the equivalent of 4 mg/day of lorazepam) and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the Screening Phase can continue these medications. No dose increases of the benzodiazepines beyond the equivalent of 4 mg/day of lorazepam or start of new benzodiazepine medications are permitted during the Screening Phase.

Safety evaluations (eg, physical examination including a brief neurologic examination, vital signs, 12-lead ECG, C-SSRS, urine drug test, alcohol breath test, and clinical laboratory tests) will be performed to assess eligibility. Menstrual cycle evaluation in premenopausal female participants

will also be performed. Adverse events will be collected from the time a signed and dated informed consent form (ICF) is obtained until the completion of the last study procedure on the final Follow-up Visit.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only after sponsor's approval as assessed on a case-by-case basis (see Section 5.4).

4.1.3. Double-blind Treatment Phase

The DB Treatment Phase starts on the day of the first dose of study intervention intake and continues until the premature discontinuation of study intervention (ie, Early Withdrawal [EW]) or the scheduled End-of-Treatment (EOT) on Day 43. Evaluations that will be performed during this phase are outlined in Section 1.3.

In the DB Treatment Phase, participants who meet all inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 ratio to receive placebo or aticaprant 10 mg for 42 days. Participants should take their assigned study intervention at home, once daily, from Day 1 to Day 42, inclusive. 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. For clinical site visits, participants will be asked not to take study intervention in the morning before they come to the site for site visit and the study intervention will be self-administered on-site and witnessed by the investigator or a properly trained designee.

Note: Participants taking benzodiazepines and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the Screening Phase can continue these medications during the DB Treatment Phase. No dose increases of benzodiazepines beyond the equivalent of 4 mg/day of lorazepam or start of new benzodiazepine medications are permitted during the 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 (Visit 2.7), including the MADRS assessment at the end of the 6-week DB Treatment Phase (ie, Day 43 MADRS) and has not discontinued study intervention early during the DB Treatment Phase.

Participants who have completed the DB Treatment Phase (Day 43) 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 double-blind treatment, whether it is in the best interest of the participant to continue treatment in the open-label long-term safety study. Participants who complete the DB Treatment Phase, are eligible, and decide to roll-over to the open-label long-term safety study are not required to complete the Follow-up Phase (see Section 1.3 and Section 10.10).

Participants that discontinue study intervention early (ie, prior to completion of Day 43 visit) or who are non-compliant to the study intervention (ie, 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 long-term safety study. Missing study intervention doses due to temporary interruption (eg, adverse event per Section 7.1.3 or other clinically relevant reason) will not be considered noncompliance.

Participants who discontinue study intervention during the DB Treatment Phase and participants who completed the DB Treatment Phase who are not rolling over to the open-label long-term safety study (67953964MDD3003) will complete the EW/EOT Visit (Visit 2.7, see Section 1.3) and will then enter the Follow-up Phase of the study (Visit 3.1, see Section 1.3 and Section 10.10).

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.

End-of-Treatment/Early Withdrawal Visit

The EOT/EW Visit (Visit 2.7) will take place on Day 43 or earlier in case of premature discontinuation of study intervention. In all cases, the EOT/EW Visit and assessments (including MADRS) will be performed per the SoA, preferably on the day after the last dose. If the EW Visit is conducted on the same day as a scheduled visit, duplicate assessments are not required (see Section 10.10).

4.1.4. Follow-up Phase

Participants will enter the Follow-up Phase and complete the Follow-up Visit (ie, Visit 3.1) unless they complete the DB Treatment Phase and decide to roll-over to the open-label long-term safety study (67953964MDD3003) or if they withdraw consent for further study assessments.

Follow-up Visit

Participants will return to the study site for a Follow-up Visit within 7 to 14 days after Visit 2.7 (EOT/EW) to assess potential withdrawal symptoms using the PWC-20 assessment. At the Follow-up Visit, safety and efficacy assessments/procedures will be completed per the SoA (see Section 1.3 and Section 10.10).

4.1.5. Open-label Long-term Safety Study

Participants who have completed the DB Treatment Phase (Day 43) 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 double-blind treatment, whether it is in the best interest of the participant to continue treatment in the open-label long-term safety study.

If a participant enters the open-label long-term safety study, the Follow-up Visit (Visit 3.1 see Section 1.3) will not be conducted.

Participants that discontinue study intervention early (ie, prior to completion of Day 43 visit) or who are non-compliant to the study intervention (ie, 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. Missing study intervention doses due to temporary interruption (eg, adverse event per Section 7.1.3 or other clinically relevant reason) will not be considered noncompliance.

4.1.6. Additional Details Related to Study Design

An IDMC will be commissioned to review safety data for this study. Refer to Committees Structure in Section 10.3.6 for details.

A diagram of the study design is provided in Section 1.2.

4.1.7. Changes in Study-related Procedures as a Result of the COVID-19 Pandemic

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 GCP, and minimize risks to study integrity, if necessary, in consultation with the sponsor, the method of assessments may be changed (eg, paper assessments replaced by electronic assessments and vice versa). In addition, site visits may be replaced with telephone, internet-based videoconferencing applications, or home visits by qualified healthcare professionals (see Section 10.9 for further details). 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.

4.2. Scientific Rationale for Study Design

4.2.1. Study Population

Up to 70% of individuals who are on antidepressant (AD) therapy are inadequately treated for their depression (Rush 2006). Suboptimal response to first-line standard-of-care antidepressant treatment for MDD remains a significant problem resulting in persistent impairment and high utilization of health care resources (Kennedy 2004). Symptoms such as loss of interest/pleasure (anhedonia), insomnia, and fatigue are reported to persist in these patients, keeping them symptomatic and leading to progressive worsening of their overall depressive symptoms (Spijker 2001; Taylor 2010; Wardenaar 2012). There remains unmet need to identify new personalized treatments addressing depression symptoms insufficiently managed by current ADs and impeding the achievement of, or prolonging the time to remission (Uher 2012).

Anhedonia, defined as an impaired capacity to experience or anticipate pleasure (Berrios 1995; Ho 2013) is a very common symptom of MDD, reported in ~75% of patients (Franken 2007) and is one of the required criteria for MDD (depressed mood and/or anhedonia) (Moayedoddin 2013; Schrader 1997). In addition to being a common symptom of MDD, as noted in the outset, it is a

persisting dimension amongst individuals with MDD with inadequate response to SSRI/SNRI (Van Roekel 2017).

Data from the Phase 2 study 67953964MDD2001 showed greater reduction in overall depression severity on the MADRS in participants with MDD treated with 10 mg aticaprant added to ongoing antidepressant, compared with those who continued their current antidepressant plus placebo. Participants with MDD with a high level of anhedonia showed better effect of improvement in overall depression, as well as improvement in items that reflect the positive affect, namely the anhedonia-specific item inability to feel, and several other items like pessimistic thoughts, lassitude, and concentration difficulties, all of which are related to the hedonic capacity as they reflect on individual's interest, engagement, motivation, and connection to the world.

The study population will include participants from the general MDD population (adults 18-64 years of age, inclusive, and elderly 65-74 years of age, inclusive) with an inadequate response to their current ongoing standard-of-care antidepressant (SSRI/SNRI) who are moderate-to-severely depressed and with either moderate-to-severe anhedonia (MDD ANH+) or with mild or no anhedonia (MDD ANH-). The primary and key secondary analyses will be conducted in the adult MDD ANH+ population and will be assessed at the end of Week 6 (Day 43). Participants with MDD ANH- and elderly participants will not be included in the primary and key secondary analyses. Criteria defining MDD ANH+ will be described in an addendum to the protocol which will be blinded to the study sites.

The proposed design for enrollment of participants with MDD ANH+ and MDD ANH- will facilitate the acquisition of efficacy data for the use of aticaprant as adjunctive therapy to the current SSRI/SNRI antidepressant treatment in improving depression symptoms in both participant populations (ie, participants with MDD without moderate-to-severe anhedonia and participants with MDD with moderate-to-severe anhedonia, with the latter being the population of interest for primary and key secondary analyses). Enrolling participants across the general spectrum of moderate-to-severe MDD will allow the study to utilize enrichment to help demonstrate antidepressant effectiveness in the subset of those with MDD ANH+ (see FDA 2019).

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

Elderly participants up to 74 years of age, inclusive, will be included in the study enrollment provided that the initial onset of symptoms of depression was before 55 years of age. The age limit (74 years, inclusive) and the requirement for first episode of MDD to be prior to age 55 is based on evidence in the literature that late life onset MDD appears to have a different pathophysiology than earlier onset MDD and is associated to a greater degree with age related changes in the brain and to a lesser extent with genetic predisposition to depression (Covinsky 2014). Furthermore, antidepressants tend to be less effective in older patients. As the elderly group of MDD patients

was not studied in the Phase 2 study, there exists an uncertainty on the expected clinical presentation and level of anhedonia severity in this age group. Therefore, participants with MDD that are 65 to 74 years of age, inclusive, will be included in the exploratory analysis but not included in the primary analysis set. The primary and key secondary analyses will be based on the adult MDD ANH+ population (18 to 64 years of age, inclusive).

Based on the completed Phase 2 study, the treatment duration of 42 days is selected to demonstrate the treatment effect of aticaprant (primary endpoint).

4.2.2. Blinding, Control, Study Phase/Periods, Intervention Groups

Participants will be randomized to receive aticaprant 10 mg or placebo. The study intervention will be administered orally as 2 film-coated tablets to be administered together, once daily, around the same time and preferably in the morning.

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. A 1:1 (adjunctive placebo: adjunctive aticaprant 10 mg) randomization ratio will be used. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints (see Section 6.3 for further details relating to measures to minimize bias: randomization and blinding).

Criteria defining MDD ANH+ and MDD ANH- subgroups are blinded to the sites and provided in an addendum to the study protocol.

Conditions to maintain the blind of MADRS raters are specified in Section 8.1.2.1. Activities employed to ensure independent confirmation of the diagnosis, severity of the depressive episode and adequacy of the current antidepressant treatment are described in Section 8.1.2.1.

4.2.3. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study, and during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Written consent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

The probability of receiving placebo and the concept of random assignment will be explained to the participant. Only participants who have not adequately responded to their current

antidepressant medication and continue to have moderate-to-severe depression and where a clinician would consider adjunctive treatment will be enrolled. Current antidepressant medication (SSRI/SNRI) will need to be continued and remain stable throughout the study and the study intervention will be added to it. Withdrawal and/or discontinuation symptoms for prohibited therapies may be challenging for some participants. However, there are a number of strategies including use of rescue medications that may be used to minimize discomfort to participants. The duration of the study is short, minimizing the time on adjunctive placebo. Participants in the study will be monitored very closely with in-person visits and remote contacts during the DB Treatment Phase. Safety evaluations will include evaluation of suicidal ideation/behavior at each clinic visit and remote contact. At any point in the study, the participant may withdraw consent, discontinue study intervention and receive approved adjunctive therapy for depression, or be removed from the study by the investigator if there are any clinical concerns and provisions for appropriate and immediate clinical triage as necessary.

The total blood volume to be collected is considered to be within the normal range allowed for this participant population over this time frame. The approximate blood volume to be collected is 123.5 mL, which will be less than a Red Cross blood donation.

An optional real-world data collection is considered for participants, agreeing via a separate ICF to the collection and use of their real-world medical data (electronic health record) in the 5 years prior to and after entry in the study.

For participants who consent to the optional collection of real-world medical data, the sponsor is committed to protect their data and privacy. Tokenization and matching procedures will be utilized to allow for those participant's medical data to be obtained without violation of participant confidentiality. Participants will be informed that consent to this part of the study is completely optional and that they can withdraw their consent at any given time. In the event of withdrawal of consent, the sponsor will remove the token generated and any associated linked real-world data. Participation in or withdrawal from this optional part of the study will not affect the participation in the main study (see Section 8.9).

All applicable applications used in this study are General Data Protection Regulation (GDPR)/Health Insurance Portability and Accountability Act (HIPAA) compliant.

4.2.4. Biomarker Sample Collection

The primary goal of the biomarker analyses is to confirm diagnostic biosignatures from blood-based biomarker panels that identify participant subgroups that respond differently to aticaprant. Secondary goals for the biomarker collections are to explore biomarkers reflective of the mechanism of action of aticaprant or that help to explain interindividual variability in efficacy, pharmacodynamics, pharmacokinetics, safety, and tolerability.

As MDD with symptoms of anhedonia may be associated with altered immune/metabolic activation patterns that are known to interact with the kappa opioid system, blood samples will be collected to measure biomarkers related to immune system activity, HPA axis activation, and KOR signaling. Biomarker levels will be combined using multimodal models and the resulting

biosignatures will be evaluated for their utility to identify population subgroups that respond differently to adjunctive aticaprant treatment. In addition, biomarkers will be explored for their utility to explain interindividual variability in clinical outcomes, pharmacokinetics. Many of these biomarkers may be influenced by stage of menstrual cycle in female participants; therefore, the menstrual cycle will be tracked in premenopausal female participants who are still having their menses during the study, by the participant diary and participant's verbal report. Biomarker samples will be collected under fasting conditions and prior to study intervention administration. The goal of the pharmacogenomic component is the identification of genetic, epigenetic, and/or transcription factors that may influence the pharmacokinetics, pharmacodynamics, efficacy, safety, or tolerability of aticaprant that are associated with MDD in general and/or specific symptoms, such as anhedonia. The DNA and RNA collections are optional procedures as detailed in a separate ICF.

The DNA, RNA, and protein biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and targeted individualized therapies.

4.2.5. Pharmacokinetic Assessments

Sparse blood samples will be collected for measurement of the plasma concentrations of aticaprant and any relevant metabolite(s), if warranted, as indicated in SoA (Section 1.3).

A population PK analysis using sparse PK data from this study will be performed at the completion of the study. The purpose of the planned population PK analysis will be to assess and confirm the PK of aticaprant in the target patient population, and to investigate the potential impact of covariates. The results of the population PK analysis will be reported separately.

In addition, an optional unscheduled blood sample may be collected for determination of plasma concentrations of aticaprant in participants who discontinue study intervention for an AESI or SAE which is related to AESI. This blood sample should be collected as close as to the AESI or AESI-related SAE occurrence, but preferably within 72 hours of the last study intervention administration. This sample is not collected in case of discontinuation due to AE, but only for AESI or AESI related SAE.

4.3. Justification for Dose

The aticaprant 10 mg/day dose selection is based on the results from the completed Phase 2a Studies FAST-MAS and Study 67953964MDD2001, as well as PK/PD and RO modeling.

Aticaprant administered at 10 mg once daily is predicted to have high kappa occupancy at C_{max} (mean peak occupancy of [redacted]%) and at trough levels (mean trough occupancy of [redacted]%).

The Phase 1 and Phase 2 program of aticaprant (healthy volunteers and participants with MDD) included participants up to 73 years of age (inclusive). The data from these studies did not yield safety and tolerability effects that might be of concern for older adults (ie, no cardiovascular effects, metabolic effects, or sedation). Considering population PK analysis from these earlier studies, age was not a significant covariate. Further, aticaprant is not renally cleared and is

primarily metabolized through CYP3A4 and CYP2C9, which may provide rationale not to expect any age effect on the PK in the elderly up to 74 years, inclusive.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last scheduled study assessment shown in the SoA for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

Treatment Completion and Study Completion Definition

Participants are considered to have completed the DB Treatment Phase if they have completed the Day 43 visit of the DB Treatment Phase (Visit 2.7), including the MADRS assessment at the end of the 6-week DB Treatment Phase (ie, Day 43 MADRS), and have not discontinued study intervention early during the DB Treatment Phase.

Participants who have completed the DB Treatment Phase (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 double-blind 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 eCRF.

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 (Visit 3.1) will not be conducted.

Participants who discontinue study intervention in DB Treatment Phase will be considered to have completed the study if they completed the Follow-up Phase (Visit 3.1), including the MADRS, DARS, and PWC-20 assessments at this visit.

5. STUDY POPULATION

Screening for eligible participants will be performed within 30 days before administration of the study intervention (refer to Section 5.4). Efforts will be made for the inclusion of a diverse study population in terms of race, gender, and ethnicity.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age

1. Male or female, aged 18 (or the legal age of consent if higher than 18 years of age, in the jurisdiction in which the study is taking place) to 74 years of age, inclusive.

Type of Participant and Disease Characteristic

2. Be medically stable on the basis of physical examination (including a brief neurological examination), medical history, vital signs (including blood pressure), and 12-lead ECG performed at screening and baseline. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their significance must be determined by the investigator and recorded in the eCRF and in the participant's source documents and initialed by the investigator.

3. Be medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, re-testing of an abnormal laboratory value(s) that may lead to exclusion will be allowed once during the Screening Phase. The participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the eCRF and in the participant's source documents and initialed by the investigator.

4. Meet DSM-5 diagnostic criteria for recurrent or single episode MDD, without psychotic features (DSM-5 296.22, 296.23, 296.32, or 296.33), based upon clinical assessment and confirmed by the SCID-CT. Participants 65 years of age or older must have had the first onset of depression prior to 55 years of age.

5. Criterion modified per Amendment 1

   5.1 Have had an inadequate response to at least 1 oral antidepressant treatment (see the inclusion criterion below), administered at an adequate dose (at or above the minimum therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current episode of depression. An inadequate response is defined as <50% reduction in depressive symptom severity but with some improvement (>0%; ie, 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. This must apply to the participant's current antidepressant treatment.

Note: Medical/pharmacy/prescription records, a letter from a treating physician, etc can be used to verify the adequacy of the current antidepressant trial.

6. Criterion modified per Amendment 1

   6.1 Is currently receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms at screening, in any approved formulation and available in the participating country/territory: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine at a stable dose (at or above the minimum therapeutic dose per MGH ATRQ) for at least 6 weeks. The current antidepressant cannot be the first antidepressant treatment for the first lifetime episode of depression.

   Note: The above SSRI/SNRI needs to be approved for the treatment of MDD according to the local label of the country/territory where the clinical site is located.

   Note: Medical/pharmacy/prescription records, a letter from a treating physician, etc can be used to verify the adequacy of the current antidepressant trial. The investigator will use this information to complete the MGH ATRQ.

   Note: Participants using fluvoxamine as background SSRI and have normal renal and hepatic function may enter the study.

7. Have a HDRS-17 total score of 20 or higher at the first and second screening interviews and must not demonstrate a clinically significant improvement (ie, an improvement of more than 20% on their HDRS-17 total score) between the first and the second independent HDRS-17 assessments.

8. Participant's current major depressive episode, and antidepressant treatment response in the current depressive episode, must all be confirmed by the Site Independent Qualification Assessment.

9. Must be an outpatient at screening.

Weight

10. Body mass index (BMI) within the range 18 and 40 kg/m^2 inclusive ($BMI = weight/height^2$).

Sex and Contraceptive/Barrier Requirements

11. A female participant of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) pregnancy test at screening and a negative urine pregnancy test pre-dose on Day 1 of the Double-blind Treatment Phase prior to randomization.

12. A female participant must be (as defined in Section 10.5):

    a. Not of childbearing potential

    b. Of childbearing potential and

        - Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 4 weeks after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.5.

13. A female participant must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of at least 1 month after receiving the last dose of study intervention.

14. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study intervention:

    - A male participant must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person.
    - A male participant who is sexually active with a woman who is pregnant must use a condom.

    Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.

15. A male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study intervention.

Informed Consent

16. Must sign an ICF indicating that the participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Medical Conditions

1. Criterion modified per Amendment 1

1.1 Have had in the current depressive episode, no response (treatment failure) to 5 or more antidepressant treatments including the current SSRI/SNRI (ie, the one presumed to be continued in the treatment phase) assessed using the MGH ATRQ.

2. Has one or more of the following diagnoses:

- A DSM-5 diagnosis (which has been the primary focus of psychiatric treatment within the past 2 years) of any of the following:
  - panic disorder
  - generalized anxiety disorder
  - social anxiety disorder
  - specific phobia

Note: These are allowed as secondary diagnoses if MDD is the primary focus of treatment according to the investigator.

- A current (in the past year) DSM-5 diagnosis of:
  - obsessive-compulsive disorder (OCD)
  - post-traumatic stress disorder (PTSD)
  - anorexia nervosa
  - bulimia nervosa

Note: These disorders need to be under control and stable for at least 1 year for the participant to be enrolled.

- A current or prior (lifetime) DSM-5 diagnosis of:
  - a psychotic disorder or MDD with psychotic features
  - bipolar or related disorders (confirmed by the SCID-CT)
  - intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319)
  - autism spectrum disorder
  - borderline personality disorder
  - antisocial personality disorder
  - histrionic personality disorder
  - narcissistic personality disorders
  - somatoform disorders

3. Has a history or evidence of clinically meaningful noncompliance with current antidepressant therapy.

4. Has a history of moderate-to-severe substance use disorder including alcohol use disorder according to DSM-5 criteria within 6 months before screening.

5. Criterion Modified per Amendment 1

   5.1 Has had in the current episode an inadequate response to adequate course of intravenous or intranasal ketamine or esketamine, electroconvulsive therapy (ie, at least 7 treatments), vagal nerve stimulation, or deep brain stimulation device.

6. Has a current homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 3 months prior to the start of the Screening Phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS), corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent), or a history of suicidal behavior within the past 6 months prior to the start of the Screening Phase. Participants reporting suicidal ideation with intent to act or suicidal behavior at baseline should be excluded.

7. Has cognitive impairment per investigator judgment that would render the informed consent invalid or limit the ability of the participant to comply with the study requirements. Participant has neurodegenerative disorder (eg, Alzheimer's disease, vascular dementia, Parkinson's disease with clinical evidence of cognitive impairment) or evidence of mild cognitive impairment (MCI). Participants aged ≥65 years: has an MMSE score <25 or <23 for those participants with less than high school equivalent education.

8. Has current, or a history (past 6 months), of seizures.

9. Criterion modified per Amendment 1

   9.1 Has clinically significant 12-lead ECG abnormalities at the start of the Screening Phase or on Day 1 of the DB Treatment Phase, prior to randomization, defined as:

   - During screening, a QT interval corrected according to Fridericia's formula (QTcF): ≥450 msec (males); ≥470 msec (female participants).

     Note: if the QTcF is prolonged on the initial 12-lead ECG at a given time point, the average QTcF of 3 12-lead ECGs, recorded 4 minutes apart, must not be ≥450 msec for males and ≥470 msec for female participants.

   - On Day 1 (pre-dose), a QT interval corrected according to Fridericia's formula (QTcF): ≥450 msec (males) or ≥470 msec (female participants) based on the site-evaluated ECG; if the QTcF is prolonged on the initial ECG, the average QTcF of 3 ECGs, recorded 4 minutes apart, must not be ≥450 msec for males and ≥470 msec for female participants.

- Evidence of second and third degree atrioventricular (AV) block, complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB).
- Features of new ischemia.
- Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs]).

10. Participant has a history of additional risk factors for Torsades de Pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome).

11. Has a history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values ≥3 × the upper limit of normal (ULN) or total bilirubin >1.5 × the ULN in the Screening Phase.

- Repeat of screening test for abnormal ALT and AST is permitted during the screening period provided per investigator discretion and provided there is an alternative explanation for the out of range value.
- For elevations in bilirubin if, in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's syndrome, the participant may participate in the study.

12. Criterion modified per Amendment 1

12.1 Has positive test result(s) for alcohol and/or drugs of abuse (eg, opiates [including methadone], cocaine, amphetamines, methamphetamines, cannabinoids, cannabidiol [CBD], phencyclidine [PCP], barbiturates, 3,4-Methylenedioxymethamphetamine [MDMA]) at screening or at baseline.

Note: One retest during screening is allowed at investigator's judgment. Tobacco and caffeine use are not exclusionary.

- Participants who have a positive test result at screening due to prescribed psychostimulants taken for any indication must discontinue the medication (if considered clinically appropriate) at least 2 weeks before Day 1 of the DB Treatment Phase (prior to randomization). The result of the Day 1 (prior to randomization) test (performed on site) for drugs of abuse must be negative for the participant to be randomized.
- Otherwise, participants who have a positive test result at screening due to prescribed/over-the-counter opiates or barbiturates may be permitted to continue in the Screening Phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the DB Treatment Phase (prior to randomization). The result of the Day 1 (prior to randomization) test (performed on site) for drugs of abuse must be negative for the participant to be randomized.
- Intermittent use of cannabinoids and/or alcohol prior to the start of the Screening Phase is not exclusionary as long as the participant does not meet the criteria for substance use disorder. A positive test for cannabinoids and/or alcohol at the start

of the Screening Phase is not exclusionary; however, a positive test result (performed on site) for either of these on Day 1 of the DB Treatment Phase is exclusionary.

- Retesting is not permitted for positive test result(s), except for reasons stated above.

13. Has a recent (last 3 months) history of, or current signs and symptoms of:

    - Clinically significant or unstable cardiovascular, respiratory, gastrointestinal, neurologic, hematologic, rheumatologic, immunologic or endocrine disorders.
    - Uncontrolled Type 1 or Type 2 diabetes mellitus. **Note:** Participants with Type 1 or Type 2 diabetes mellitus who are controlled (hemoglobin A1c ≤9.0%) may be eligible to participate if otherwise medically healthy, and if on a stable regimen of glucose-lowering medications for at least 2 months prior to screening).

14. Has current signs/symptoms of hypothyroidism or hyperthyroidism. For participants with a history of thyroid disease and for participants who, regardless of thyroid history have the thyroid-stimulating hormone (TSH) value out of range, a free thyroxine (FT_4) test will be conducted. If the FT_4 value is abnormal and considered to be clinically significant (after discussion with the sponsor's study responsible physician/scientist or designee) the participant is not eligible.

    Participants with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones need to be on a stable dosage for 3 months prior to the start of the Screening Phase. Participants taking thyroid supplementation for antidepressant purposes are not allowed in the study.

15. Has Cushing's disease, Addison's disease, primary amenorrhea, or other evidence of significant medical disorders of the hypothalamic-pituitary-adrenal axis.

16. Has severe renal impairment (creatinine clearance <30 mL/min).

17. Has significant medical illness, particularly unstable medical problem (to be reviewed with the sponsor's medical monitor).

18. Has a known history (past 6 months) of peptic ulcer, or history (lifetime) of upper gastrointestinal bleeding, or known untreated *Helicobacter pylori* infection, or a diagnosis of Zollinger-Ellison syndrome (ZES).

19. Has a history of malignancy within 5 years before the start of the Screening Phase (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that, in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence).

20. Has known allergies, hypersensitivity, or intolerance to aticaprant or its excipients (refer to the IB).

Prior/Concomitant Therapy

21. Has taken any prohibited therapies that would not permit dosing on Day 1.

22. Is taking a total daily dose of benzodiazepine greater than the equivalent of 4 mg/day of lorazepam at the start of the Screening Phase.

23. Participants should not take any prohibited medication or food supplements as indicated in Section 6.8.

Prior/Concurrent Clinical Study Experience

24. Ongoing psychological treatments (eg, Cognitive Behavioral Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy, etc), initiated within 6 weeks prior to start of screening.

    Note: a participant who has been receiving ongoing psychological treatment for a period of greater than 6 weeks is eligible, if the investigator deems the psychological treatment to be of stable duration and frequency.

25. Has received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 60 days or 10 half-lives, whichever is longer, before the start of the Screening Phase or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational medication) in the previous 1 year before the start of the Screening Phase or is currently enrolled in an investigational study.

Other Exclusions

26. Is a female participant who is pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 6 weeks after the last dose of study intervention.

27. Plans to father a child while enrolled in this study or within 3 months after the last dose of study intervention.

28. Has any condition or situation/circumstance for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

Diagnostic Assessments

29. Has a diagnosis of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus (HIV) testing is not required for this study.

Other Exclusions

30. Employee of the investigator or study site with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening and/or Day 1 prior to randomization (as applicable). If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that the participant no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4 describes options for re-testing. The required source documentation to support meeting the enrollment criteria are noted in Section 10.3.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the study to be eligible for participation:

1. Participants should not take any prohibited medication or food supplements. Refer to Section 6.8 for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.3.1. Meals and Dietary Restrictions

1. The use of limited amounts of alcohol (up to 2 standard drink consumptions daily) will be allowed but not within 24 hours before any study visit. A standard drink is defined as: a 350 mL glass of 5% alcohol-by-volume (ABV) beer (1.7 units), a 150 mL glass of 12% ABV wine (2 units), or a 45 mL glass of a 40% ABV (80 proof) spirit (1.7 units).

2. Should not consume food or beverages containing grapefruit juice, Seville oranges (including any orange marmalade), or quinine (eg, tonic water) from 24 hours (72 hours in the case of grapefruit juice and Seville oranges) before the first dose of study intervention and throughout the duration of the study until the last dose of study intervention.

5.3.2. Activity

1. Participants should abstain from strenuous exercise within 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study (eg, watching television, reading).

2. Participants should be advised not to donate blood during the study and for at least 3 months after completion of the study.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study site contact for completeness. When available, the investigator may generate screening and enrollment logs directly from the interactive web response system (IWRS).

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent.

The sponsor will evaluate and approve/reject requests to rescreen an individual participant on a case-by-case basis.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Designation	Product
Investigational Medicinal Product	Aticaprant (JNJ-67953964)/Placebo
Non-investigational Medicinal Product/Auxiliary Medicinal Product	Current SSRI/SNRI antidepressant *

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

* Current antidepressant therapy must be continued throughout the entire study, at the same dose, every day without change, and at approximately the same time of the day as prior to entering the study. The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. For further information regarding their use, refer to the relevant local prescribing information.

Study intervention administration must be captured in the source documents and the eCRF.

Aticaprant will be dispensed as film-coated tablets of 10 mg. Placebo will be supplied as matching tablets.

All participants will receive 2 tablets (1 large tablet and 1 small tablet) to be taken daily, irrespective of treatment assigned.

The study intervention (aticaprant 10 mg or placebo) will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

The study intervention will be provided as a double dummy pack type in blister kits (otherwise described as “container” throughout the document) identified by a study number. The labels will contain information to meet the applicable regulatory requirements.

During the DB Treatment Phase, all participants must take their assigned study intervention, supplied as 2 oral film-coated tablets, once daily, around the same time and preferably in the morning. Participants will take 1 large tablet and 1 small tablet. The first dose will be taken by the participant at the study site on Day 1 of the DB Treatment Phase after randomization and witnessed by the investigator or a properly trained designee. Thereafter, study intervention will be taken at home by the participant for daily self-administration until the next clinical site visit. For clinical site visits, participants will be asked not to take study intervention in the morning before they come to the site for the visit and the study intervention will be self-administered on-site and witnessed by the investigator or a properly trained designee. The investigator or designated study personnel will maintain a log of all study intervention dispensed and returned. Drug supplies will be inventoried and accounted for throughout the study. Tablet counts of study intervention will be performed at each clinical visit during the treatment phase of the study.

If a scheduled dose is missed, participants are advised not to administer 2 doses at a time the next day. The dose will be skipped. Information about the missing dose should be recorded in participant diaries and in the eCRF study intervention log.

Study site personnel will instruct participants on how to store the study intervention for at-home use. A participant diary to capture study intervention use will be provided.

All participants will continue their current SSRI/SNRI antidepressant (the Non-investigational Medicinal Product) 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. The participant's use of their current SSRI/SNRI antidepressant therapy during the study should be captured by the participant using a medication diary (see Section 6.8.1).

If appropriate, additional details may be provided in a pharmacy manual/study site investigational product manual that is provided separately and noted in Section 8.

Description of Interventions

Group/Arm Name	Group/Arm A	Group/Arm B
Intervention Name	Aticaprant/JNJ-67953964	Placebo
Dose Formulation	Film-coated tablet	Matching placebo
Unit Dose Strength(s)	Available unit dose strength: 10 mg	Not applicable
Dosage Level(s) and Frequency	Participants will receive 10 mg aticaprant orally once daily in addition to their current antidepressant (SSRI/SNRI) therapy which will be continued during the entire study	Participants will receive matching oral placebo once daily in addition to their current antidepressant (SSRI/SNRI) therapy which will be continued during the entire study
Route of Administration	☒ Oral ☐ IV infusion ☐ IV injection ☐ Intramuscular ☐ Other	☒ Oral ☐ IV infusion ☐ IV injection ☐ Intramuscular ☐ Other
Dosing Instructions	Participants must take 2 (ie, 1 small and 1 large) oral film-coated tablets once daily, around the same time and preferably in the morning	Participants must take 2 (ie, 1 small and 1 large) oral film-coated tablets once daily, around the same time and preferably in the morning
Use	☒ Experimental ☐ Background intervention ☐ Challenge agent ☐ Diagnostic ☐ Other	☐ Experimental ☒ Placebo comparator ☐ Active comparator ☐ Sham comparator ☐ Rescue medication ☐ Background intervention ☐ Challenge agent ☐ Diagnostic ☐ Other
Investigational Medicinal Product (IMP)	☒ Yes ☐ No	☒ Yes ☐ No
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	☐ Yes ☒ No	☐ Yes ☒ No

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

All study intervention will be stored in a secure area with restricted access. Tablets must be stored at controlled room temperatures as indicated on the product specific labeling.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

Study intervention must be handled in strict accordance with the protocol and as indicated on the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Study intervention must be dispensed under the supervision of the investigator or a qualified member of the study site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor. Further guidance and information for the final disposition of unused study intervention are provided in the study site investigational product and procedures manual (IP manual).

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 2 intervention groups in a 1:1 ratio based on a computer-generated randomization schedule implemented in the IWRS before the study. Separate randomization lists for MDD ANH+ and MDD ANH- will be generated before the study by, or under the supervision of the sponsor. For each list, the randomization will be balanced by using randomly permuted blocks and will be stratified by country/territory and age group (adults [18 to 64 years of age, inclusive], elderly [65

to 74 years of age, inclusive]). Based on this randomization code, the study intervention will be packaged and labeled for each participant. The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

Participants will be randomized to receive aticaprant 10 mg or placebo. The study intervention will be administered orally as 2 film-coated tablets, to be administered together, once daily, around the same time and preferably in the morning.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, study intervention plasma/serum concentrations, study intervention preparation/accountability data, intervention allocation, and biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind must not be broken until all participants have completed the study and the database is finalized. The investigator may, in an emergency, determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee, if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible.

The date and time of unblinding must be documented in the IWRS, and reason for the unblinding must be documented in the appropriate section of the eCRF, and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded should continue to return for the EOT/EW and follow-up assessments as indicated in Section 7.1.

6.4. Study Intervention Compliance

Except for on-site clinic visits, the study intervention will be self-administered by participant at home daily around the same time and preferably in the morning from Day 1 to Day 42 of the DB Treatment Phase. The first dose will be taken on Day 1 on-site post randomization and will be

witnessed by the investigator or a responsible designee. At subsequent clinical visits, study intervention will be self-administered on-site and witnessed by the responsible site staff personnel. Participants will receive instructions on compliance with the study intervention treatment. During the course of the study, the investigator or designated study site personnel will be responsible for providing additional instruction to re-educate any participant to ensure compliance with taking the study intervention. Participant diary will be provided to capture study intervention use and reviewed by the investigator or a responsible designee as specified in the SoA (see Section 1.3).

The number of study intervention tablets dispensed for self-administration by participants at home will be recorded and compared with the number returned during postbaseline visits. Participants with repetitive noncompliance to the study intervention in the DB Treatment Phase (ie, have missed either 4 or more consecutive doses of study intervention or a total of 8 or more doses during the DB Treatment Phase) may be withdrawn from study intervention (see Section 7.1). Missing study intervention doses due to temporary interruption (eg, adverse event per Section 7.1.3 or other clinically relevant reason) will not be considered noncompliance.

The investigator or designated study site personnel will maintain a log of all study intervention dispensed and returned. Drug supplies for each participant will be inventoried and accounted for throughout the study. If appropriate, additional details may be provided in a site investigational product manual that is provided separately and noted in Section 8.

6.5. Dose Modification

This is a fixed dose study of 10 mg aticaprant or placebo. No dose modifications in study intervention are permitted during the DB Treatment Phase.

6.6. Continued Access to Study Intervention After the End of the Study

Participants who have completed the DB Treatment Phase 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 study. Please refer to the 67953964MDD3003 protocol for full details and criteria for rolling over to this open-label study.

Participants who receive at least 1 dose of study intervention in the DB Treatment Phase and are not enrolling in the open-label long-term safety study 67953964MDD3003 will proceed to the Follow-up Phase. The study intervention will not 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 the participant's treating physician.

Participants should continue their treatment with the current (SSRI/SNRI) antidepressant without change until the Follow-up phase to allow for assessment of withdrawal symptoms using the PWC-20 assessment.

6.7. Treatment of Overdose

For this study, any dose of aticaprant greater than 6 tablets (3 small and 3 large) within a 24-hour time period will be considered an overdose. The sponsor does not recommend specific treatment for an overdose

In the event of an overdose, the investigator or treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention must be interrupted.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until aticaprant can no longer be detected systemically (at least 2 days).
- Obtain a plasma sample for PK analysis within 2 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.
- Overdose should be reported in the eCRF as an AE.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Prestudy non-antidepressant therapies administered for up to 30 days before the start of the Screening Phase must be recorded at the start of this phase. Ongoing (chronic or occasional) administration and known prior (past 6 months) use of proton pump inhibitors (PPIs), H2 blockers or other gastroprotective agents, nonsteroidal anti-inflammatory drugs (NSAID), or aspirin, must be recorded (eg, dose, duration, reason) under Concomitant Therapies in the eCRF.

All antidepressant treatment(s), taken during the current depressive episode (ie, including those taken more than 30 days prior to the start of the Screening Phase) will be recorded at the start of the Screening Phase. This includes non-pharmacological treatments (eg, psychotherapy, transcranial magnetic stimulation [TMS], etc). Antidepressant pharmacological treatments which are not listed on the MGH ATRQ but were used, or currently being used, as antidepressant treatment in the current depressive episode must be recorded in the 'Concomitant Therapy' eCRF.

Concomitant therapies must be recorded throughout the study, beginning with signing of the ICF and continuing up to the last study visit. Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study. Information on concomitant therapies should also be obtained beyond this time only in conjunction with new or worsening AEs until resolution of the event.

Participants should continue to take their permitted concomitant medications at their regular schedule; however, restrictions as outlined in Section 6.8.2 and Section 10.7 should be taken into

account. Participants taking antidepressant medications which are not listed on the MGH ATRQ (for a complete list of antidepressant medications, please refer to Section 10.7 for a list of medications used for the treatment of depression to be discontinued during the Screening Phase) at entry will have these medications tapered (if applicable) and discontinued during this phase, per the local prescribing information or clinical judgment. Additionally, any medication that is listed on the MGH ATRQ and taken in addition to the current SSRI or SNRI which will be continued in the study treatment phase including medications taken for reasons other than depression (eg, insomnia or anxiety) should be continued during the Screening Phase but must be discontinued before the start of the DB Treatment Phase.

Tapering and discontinuation of prohibited therapies should be initiated after completion of the second HDRS-17 assessment (see Section 1.3) and the SIQA and confirmation these were passed. Eligible participants who do not require a tapered discontinuation of their prohibited treatment(s) can proceed to the baseline randomization visit.

This study allows the use of locally approved (including emergency use-authorized [or country/territory-specific equivalent emergency use approved]) COVID-19 vaccines. 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. If any vaccines (COVID-19 or other vaccines, eg, influenza) are administered, these should be recorded in the source documents and entered in the eCRF.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as psychotherapy electrical stimulation, acupuncture, special diets, and exercise regimens) different from the study intervention must be recorded in the eCRF. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study, unless permitted by protocol.

6.8.1. Current (SSRI/SNRI) Antidepressant Therapy

Throughout the study, all participants will need to 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 study) on which they have had inadequate response at the time of screening.

All participants will continue their current antidepressant (SSRI/SNRI) therapy during the Screening and DB Treatment Phase. The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. Participants will only continue one of these allowed antidepressants at an adequate and tolerated dose during the study. No changes in current antidepressant or dose are permitted from screening until the end of the DB Treatment Phase.

Participants will receive instructions on compliance with their current oral antidepressant treatment (SSRI/SNRI). During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any participant to ensure compliance with taking the current oral antidepressant (SSRI/SNRI). During the Screening Phase, compliance to the current antidepressant treatment must be confirmed by documented records (eg,

medical/pharmacy/prescription record, a letter from a treating physician, etc). During the DB Treatment Phase, the compliance to the SSRI or SNRI (the one that is continued in this phase) will be assessed by documented records (medical/pharmacy/prescription records, pill counts etc). In absence of other options to assess compliance, blood or urine levels can be used by the site to evaluate the adherence to the antidepressant treatment. A participant's diary will be provided to capture the current oral antidepressant (SSRI/SNRI) use (see Section 1.3).

The current antidepressant will not be provided by the sponsor. Participants or their insurance will be responsible for the cost of the SSRI/SNRI; the sponsor will not be responsible for the cost unless otherwise specified by local regulations. If during the study, the participant can no longer provide for the SSRI/SNRI, this issue will need to be discussed with the sponsor's medical monitor.

6.8.2. Prohibited Therapies

A list of prohibited concomitant therapies is provided in Section 10.7. This list is not all-inclusive; if necessary, please contact the medical monitor for any questions regarding a medication(s).

Please refer to the local prescribing information of the participant's non-study medications for information regarding prohibited concomitant medications.

Except where specifically noted, the prohibited medications listed in Section 10.7, are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of study intervention until after the last dose of study intervention.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Refer to Section 5.1 (Inclusion Criteria) and Section 5.2 (Exclusion Criteria) for information regarding contraception requirements and to Section 5.3 (Lifestyle Considerations) for additional information on prohibition and restrictions.

In addition:

- Electroconvulsive therapy (ECT), deep brain stimulation (DBS), TMS, and vagus nerve stimulation (VNS) are prohibited from study entry through the end of the DB Treatment Phase.
- Participants taking benzodiazepines and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the Screening Phase can continue these medications during the DB Treatment Phase. No dose increases beyond the equivalent of 4 mg/day of lorazepam or start of new benzodiazepine medications are permitted during the DB Treatment Phase.
- A positive urine drug test for use of PCP, or cocaine from Day 1 of the DB Treatment Phase through the final visit in the DB Treatment Phase will lead to discontinuation from the study (see Section 7).
- Participants who have been receiving ongoing psychological treatment (eg, Cognitive Behavioral Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy, etc) for a period of greater than 6 weeks prior to start of screening can continue receiving the

psychotherapy. Start of new psychotherapy or change in existing therapy is not allowed from the start of the Screening Phase through to the final visit in the DB Treatment Phase.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant discontinues study intervention or withdraws from the study before the end of the DB Treatment Phase, the early withdrawal assessments should be obtained.

All participants who prematurely discontinue study intervention during the DB Treatment Phase will have an EOT/EW Visit (Visit 2.7 in the SoA, see Section 1.3) and a Follow-up Phase (Visit 3.1 in the SoA) performed.

7.1. Discontinuation of Study Intervention

A participant will not be automatically withdrawn from the study if he or she has to discontinue study intervention before the end of the DB Treatment Phase.

A participant's study intervention will be discontinued for any of the following reasons:

- Lack of Efficacy, per investigator's judgment.
- The investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention, including, but not limited to:
  - Signals indicative of acute suicidal ideation with a clear plan or intent at any time during the study; the participant should be referred to appropriate medical/psychiatric care.
  - AST and/or ALT >5 x ULN (confirmed by repeat testing).
  - AST and/or ALT ≥3 x ULN and total bilirubin ≥2 x ULN (confirmed by repeat testing).
- The participant becomes pregnant. Refer to Section 10.5.
- Major protocol deviation (to be assessed on a case-by-case basis).
- Study intervention blind is broken.
- Lost to follow-up.
- Positive urine drug test for PCP or cocaine at any time point during the study.

When a participant withdraws, the reason for withdrawal is to be documented in the eCRF and in the source document.

Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

7.1.1. Liver Chemistry Stopping Criteria

Stopping of study intervention for abnormal liver tests is required by the investigator when either a participant meets ALT or AST elevations >5 x ULN at least twice over a 2-week period, AST and/or ALT ≥3 x ULN and total bilirubin ≥2 x ULN (confirmed by repeat testing), or one of the conditions outlined in Section 10.6, or in the presence of abnormal liver chemistries not meeting

protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline) in QT interval corrected using Fridericia's formula (QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding must be reported as an AE. The QTc stopping criteria apply only to the DB Treatment Phase and not at screening or baseline.

A participant who meets either of the following criteria (after baseline, Day 1, pre-randomization) based on the average of triplicate ECG readings will be withdrawn from study intervention:

- QTcF change from baseline is ≥60 msec AND QTcF >480 msec

OR

- QTcF >500 msec.

7.1.3. Temporary Interruption, Restart or Rechallenge

The following guidance should be considered during the study treatment phase if a participant reports moderate/severe upper GI symptoms suggestive of ulcer or heartburn lasting more than 3 days and with no potential alternative causes according to clinical judgment:

- The oral study intervention should be interrupted.
- If the symptoms resolve with the interruption, treatment may be restarted.
- If the symptoms worsen or do not resolve with the interruption of the oral study intervention, the participant should be referred to a gastroenterologist, other relevant specialist, or primary care physician for a follow-up assessment. After the assessment, if recommended by the referring physician, and considered appropriate according to the clinical judgment of the investigator, the participant may continue with dosing.
- If moderate/severe upper GI symptoms suggestive of ulcer or heartburn re-occur with rechallenge, consider treatment discontinuation and refer to a gastroenterologist, other specialist or primary care physician for further follow-up assessments.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up,
- Major Protocol Deviation (to be assessed on a case-by-case basis),
- Withdrawal of consent (**Note:** "Withdrawal of Consent" should only be selected as a reason for withdrawal if the participant does not agree to any further study assessments or procedures.

If the participant is agreeable to participating in the EOT/EW Visit and the Follow-up Phase, another reason for withdrawal should be selected),

- Positive urine drug test for PCP or cocaine at any time point during the study,
- Death.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document.

Any participant who withdraws after receiving the study intervention will have an early withdrawal evaluation.

Withdrawal of Consent

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed unless the participant agrees to take part in the EOT/EW Visit. A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

Every effort will be made in the study to ensure withdrawal of consent is not selected as a reason for discontinuation when in fact the participant withdrew for an identifiable reason (eg, due to an AE or withdrew due to lack of efficacy). Participants who wish to withdraw from the study should be asked if they are agreeable to continue to an early withdrawal visit (if withdrawing from the DB Treatment Phase) and the Follow-up Phase, or to be contacted to collect follow-up information. Participants who are not agreeable to follow-up contact will be withdrawn from the study as "withdrawal of consent." Participants who no longer wish to take study intervention but agree to provide information will be withdrawn from the DB Treatment Phase with the reason noted as "Other" and will specify the reason why. For a participant who does "withdrawal of consent," it is recommended that the participant withdraw consent in writing; if he/she refuses or is physically unavailable, the study site should document and sign the reason for the participant's failure to withdraw consent in writing and maintain it with the source records. The investigator will be responsible for making all required notifications to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Participants who withdraw will not be replaced.

Managing Missing Data

For any participant who has not completed the DB Treatment Phase (Day 43 visit or at least Day 43 MADRS assessment), an EOT/EW Visit should be conducted as soon as possible, preferably within one day of the last dose of study intervention.

If a participant discontinues from the study in the DB Treatment Phase (ie, prior to completion of the Day 43 visit), an EOT/EW Visit (Visit 2.7) should be conducted as soon as possible, preferably the day after the last dose of study intervention, and within 1 week of the date of discontinuation, followed by the Follow-up Phase (Visit 3.1). Participants who prematurely discontinue study intervention for any reason before completion of the DB Treatment Phase will not be considered to have completed the DB Treatment Phase of the study.

Participants that discontinue study intervention early (ie, prior to completion of the Day 43 visit) or who are non-compliant to the study intervention (ie, have missed either 4 or more consecutive doses of study intervention or a total of 8 or more doses during the DB Treatment Phase; see Section 6.4) will not be eligible to participate in the open-label study.

Missing data in clinical trials can lead to problems that undermine the scientific credibility of causal conclusions. The most common reason for missing data is participants who discontinue the assigned study intervention because of AEs, lack of tolerability, lack of efficacy, or inconvenience. To reduce missing data in this study, if a participant discontinues the DB study intervention for reasons other than withdrawal of consent, he/she will be expected to complete the Follow-up Phase (Visit 3.1).

7.2.1. Withdrawal From the Use of Research Samples

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Genetic Research Samples

A participant who withdraws their consent from the use of pharmacogenomics and epigenetic (DNA, RNA) samples obtained in the study will have the following options regarding the optional research sample:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Details should be provided in a separate ICF for optional research samples.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Section 10.3.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

To ensure access to participants during follow-up, the study sites should attempt to obtain both primary and secondary telephone contact numbers (eg, home, work, and mobile phone numbers), as well as other contact information (eg, email addresses) from participants before randomization. In addition, the study site should emphasize the importance of follow-up information to the participant before randomization. The measures taken to follow-up must be documented in the eCRF.

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant where possible (3 telephone calls, emails, fax, and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant's medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA (Section 1.3) summarizes the frequency and timing of efficacy, safety, laboratory, clinical pharmacology, pharmacogenomics and epigenetic, and biomarker, measurements applicable to this study.

Order of Assessments

All MADRS assessments will be performed by qualified site-based raters using videoconferencing which provides opportunity to schedule and complete the MADRS assessment before or after the on-site visit but respecting the visit window. To reduce the time spent by a participant on-site during the clinical visit, sites are recommended for clinical visits in the study treatment period with

several procedures to consider scheduling and conducting the MADRS assessment (with videoconferencing) outside of the on-site visit.

Patient-reported outcome (PRO) assessments should be completed by participants in the order stated in the SoA and in a language in which the participant is fluent and literate. Study personnel will instruct participants how to self-complete the PRO assessment (see Section 10.8) and further details are provided in a separate manual provided to the site (see below in Study -Specific Materials). When possible, PRO assessments that have not been completed at home prior to the study visit but are conducted when the participant is on site, together with the on-site PRO assessments, should be completed before any tests, procedures, or other consultations to prevent influencing participant perceptions. However, during site visits with fasting blood sampling, this may not be possible and for these visits it is recommended that procedures should be performed in the following sequence:

- Blood and urine collection (when in fasted condition), dosing, breakfast, PROs, interview with site-based rater (SIGMA via videoconference, if not completed before the actual visit, CGI-S), C-SSRS, and safety assessments. Blood collections for PK and PD assessments should be kept as close to the specified time as possible.
- Twelve-lead ECG readings will be performed both pre-dose and post-dose at Visit 2.1 (Day 1). Additional 12-lead ECG readings will be taken 1 to 4 hours post-dose at Visit 2.5 (Day 29) and Visit 2.7 (EOT/EW). If blood sampling or vital sign measurement is scheduled for the same time point as 12-lead ECG recording, the procedures are recommended to be performed in the following order: 12-lead ECG, vital signs, blood draw.
- Additional serum (by central laboratory) or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The total blood volume for the study is approximately 123.5 mL (21.0 mL for safety, 24.0 mL for pharmacokinetics, 8.0 mL for antidepressant compliance, 2.0 mL for pharmacogenomics and epigenetics, 10.0 mL for RNA samples and 60.0 mL for biomarkers).

For each participant, the maximum amount of blood drawn from each participant in this study will not exceed 150.0 mL.

The total blood volume to be collected from each participant will be approximately 123.5 mL.

Volume of Blood to be Collected from Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post-intervention assessments)			
- Hematology and serum chemistry[b]	4.5	3	13.5
- TSH/FT_4	2.5	1	2.5
- Lipid Panel	2.5	1	2.5
Efficacy			
Pharmacokinetic samples	4.0	6	24.0
Antidepressant compliance	2.0	4	8.0
Biomarker samples (plasma and serum)	20.0	3	60.0
RNA samples[c]	5.0	2	10.0
DNA sample[c]	3.0	1	3.0
Approximate Total[d]	43.5	21	123.5

Abbreviations: DNA = deoxyribonucleic acid; FT_4 = free thyroxine; HbA1c = Hemoglobin A1c; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; β-hCG = beta human chorionic gonadotropin.

a. Calculated as number of samples multiplied by amount of blood per sample.
b. HbA1c is taken with hematology if at the same visit.
   Serum β-hCG pregnancy test at Visit 1.1 is taken with serum chemistry.
   Lipid testing is taken with serum chemistry at Visit 1.1, 2.1 and 2.7.
c. Blood samples will be collected only from participants who have consented to provide an optional DNA and RNA sample[s] for research.
d. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Note: An indwelling intravenous cannula may be used for blood sample collection.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form.

Refer to the SoA in Section 1.3 for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- IB for aticaprant
- Data Science Materials
- Investigational Product (IP) Binder, including the IP Procedures Manual
- Laboratory manual and materials
- Guidance on the recommended order of study procedures
- MGH ATRQ Guidance Document
- 12-lead ECG equipment and associated materials (eg, manual)

- Rater qualifications/requirements for select clinician-administered assessments
- Clinician-administered and patient-reported outcome assessments:
  - Paper versions, as applicable
  - Electronic devices and associated materials
- Procedural documents for SIQA
- Procedural documents for independent, central rater and site-based rater interviews
- eCRF Completion Guidelines
- Sample ICF
- IWRS Manual
- Participant recruitment materials
- Participant diaries
- Engage: A Smartphone Application used for video and audio teleconferencing

The Engage application does not place cookies on the participant's device nor requires access to personal or GPS data. The application uses the camera and microphone only during an active call and it does not use the device's inbuilt possibilities for autofill, photo, or GPS. The application does use the inbuilt possibilities for video capabilities. The application has no access to device storage, photos, videos or other data on the device. All audio/video is captured on the vendor's conduit server only.

This list is not all-inclusive.

8.1. Assessments

The following assessments will be performed at the timepoints indicated in the SoA (Section 1.3). To minimize the risk of unblinding the treatment assignment, different site raters will perform efficacy and safety assessments; clinicians who perform the MADRS assessments will not be involved in assessing AEs.

8.1.1. Screening Assessments

The following screening assessments will be administered by independent remote raters:

- SIQA
- HDRS-17

The following assessments will be performed by appropriately trained and certified investigators or designees:

- SCID-CT
- MGH ATRQ
- MMSE (safety assessment to be performed in participants of 65 to 74 years of age, inclusive)

8.1.1.1. 17-item Hamilton Depression Rating Scale (HDRS-17)

The HDRS-17 is a clinician-administered rating scale designed to assess the severity of symptoms in participants diagnosed with depression (Hamilton 1960). It is the most widely used symptom severity measure for depression. It contains 17 items pertaining to symptoms of depression experienced over the past week. Items are scored on a Likert scale of 0-4 or 0-2 depending on the item with a possible range of 0-54. The original HDRS-17 scale lacks instructions for administration and clear anchor points for the assignment of severity ratings. For this reason, the structured interview guide version of the HDRS-17 (the Structured Interview Guide for the Hamilton Depression Scale [SIGH-D]) (Williams 1988) will be used in the current study to facilitate and standardize gathering clinical information from the participant. HDRS-17 assessments will be administered by independent remote raters and will be audio-recorded for the purpose of quality monitoring.

8.1.1.2. Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH ATRQ)

The MGH ATRQ is used to determine treatment response and resistance in MDD. It evaluates the adequacy of duration and dose of all antidepressant medications used for the current major depressive episode. The MGH ATRQ defines 6 weeks on an adequate dose of antidepressant medication as an adequate duration of treatment. It also provides specific operational criteria for adequate dosage for each of the most commonly used antidepressants. In addition, the MGH ATRQ assesses the degree of improvement on a scale from 0% (not improved at all) to 100% (completely improved). The MGH ATRQ will be completed by the clinician in collaboration with the participant. Two different versions of the scale will be used: for participants 18 to 64 years of age, inclusive and for participants 65 to 74 years of age, inclusive.

8.1.1.3. Structured Clinical Interview for DSM-5 Axis I Disorders – Clinical Trials Version (SCID-CT)

The Structured Clinical Interview for DSM-5 Axis I Disorders – Clinical Trials Version (SCID-CT) is a semi-structured interview guide for making the major DSM-5 diagnoses. It is administered by a clinician or trained mental health professional who is familiar with the DSM-5 classification and diagnostic criteria as well as clinical diagnostics.

8.1.1.4. Site Independent Qualification Assessment (SIQA)

The SIQA is used to confirm the diagnosis of depression and eligibility for the study. Independent remote psychiatrists/psychologists will perform the qualification assessment for all participants to confirm the validity of a diagnosis of depression, the severity of the depressive symptom and eligibility for the study (Targum 2008). The interviewer will review participant screening information and conduct a live, remote interview with the participant. This interview will include conducting HDRS-17 during screening. Further information regarding this assessment will be provided to sites in a separate document.

8.1.2. Efficacy Assessments

The following efficacy assessments will be performed:

- MADRS (performed using the Structured Interview Guide for the MADRS [SIGMA])
- CGI-S
- RLT (to be performed in English-speaking countries/territories)

The following efficacy assessments are PROs and will be completed by the participants:

- SHAPS
- DARS
- PGI-S (anhedonia)
- PHQ-9
- PGI-S (depression)
- PROMIS-APS 8a
- QLDS
- EQ-5D-5L
- GAD-7
- PGI-C (anhedonia)

All PRO instruments will be provided in the local language in accordance with local guidelines.

All PRO instruments will be available for regulators and for IRB/IEC submissions and will be provided separately in a companion manual with the instruments that will be submitted with the protocol.

The PRO and AE data will not be reconciled with each other.

8.1.2.1. Montgomery-Åsberg Depression Rating Scale (MADRS)

The primary efficacy evaluation will be the MADRS total score. The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. 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), for a total score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

The MADRS will be performed by site-based raters via video teleconferencing during the study using the Structured Interview Guide for the MADRS (SIGMA). The typical recall period for the MADRS is 7 days and will be used for the primary efficacy evaluation. To minimize the risk of unblinding the treatment assignment, different site raters will perform efficacy and safety assessments; clinicians who perform the MADRS assessments will not be involved in assessing AEs. MADRS assessments may be video-recorded for the purpose of quality monitoring.

CCI [redacted]

8.1.2.2. Snaith-Hamilton Pleasure Scale (SHAPS)

CCI [redacted]

8.1.2.3. Dimensional Anhedonia Rating Scale (DARS)

The 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. The instrument is scored as a total sum of all items (range 0-68) with higher scores reflecting increased motivation, effort and pleasure (ie, less anhedonia).

8.1.2.4. Clinical Global Impression-Severity (CGI-S)

CCI [redacted]

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

CCI [redacted]

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

CCI [redacted]

8.1.2.7. Patient Health Questionnaire, 9-item (PHQ-9)

CCI [redacted]

8.1.2.8. PROMIS Short Form v2.0 - Ability to Participate in Social Roles and Activities - 8a (PROMIS-APS 8a)

CCI [redacted]

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

CCI [redacted]

8.1.2.10. Quality of Life in Depression Scale (QLDS)

CCI [redacted]

CCI [redacted]

8.1.2.11. European Quality of Life, 5 Dimension, 5-Level (EQ-5D-5L) Questionnaire

CCI [redacted]

8.2. Safety Assessments

An IDMC will be commissioned for this study to periodically review safety data.

Details regarding the IDMC are provided in Section 10.3.6, Committees Structure.

Physical examination, body weight, BMI, vital signs (including blood pressure, pulse/heart rate, and temperature measurements), 12-lead ECG, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), pregnancy testing (for female participants of childbearing potential) will be performed throughout the study to monitor participant safety.

Additional blood and urine samples may be taken, or vital signs and 12-lead ECGs recorded at the discretion of the investigators as needed.

Menstrual cycles will be tracked in premenopausal female participants who are still having their menses during the study, using a participant diary and participant's verbal report.

Adverse events (AEs), including TEAEs will be evaluated throughout the course of the study. Clinically relevant TEAEs of special interest will be examined separately and grouped in the following categories as defined by the Standardized Medical Dictionary for Regulatory Activities (MedDRA) (version 23.0, or above if applicable).

Adverse events will be reported and followed by the investigator as specified in Section 8.3 and Section 10.4.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached. Narrative descriptions will be provided for deaths, participants with serious adverse events, and participants who discontinued study intervention due to an adverse event.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

The study investigator, or other authorized and appropriately qualified designee, will perform the physical examinations that will include assessment of sensation, level of alertness, ataxia, tremor, and other routine components of a brief neurological examination. Height will be measured at screening only. Body weight will be measured at screening and throughout the study according to the SoA (see Section 1.3).

Body weight should be measured using a calibrated scale at each indicated visit as outlined in the SoA (see Section 1.3). Participants should be weighed at approximately the same time of day on the same scale, wearing lightweight clothing without shoes; they will be instructed to empty their bladders before being weighed.

8.2.2. Vital Signs

Blood pressure and pulse/heart rate measurements will be assessed with the participant in a sitting position using a completely automated device. Manual techniques will be used only if an automated device is not available. Sitting blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

In addition, oral or tympanic temperature will be measured. In the places where oral or tympanic temperature are not standard practice, axillary temperature can be used. The same temperature measure should be used throughout the study.

8.2.3. Electrocardiograms

Twelve-lead ECGs, intended for safety monitoring, will be recorded in a supine position so that the different ECG intervals (RR, PR, QRS, QT) can be measured. The 12-lead ECG will be recorded at screening and baseline (Day 1, pre-randomization) until 4 regular consecutive complexes are available in good readable quality.

Notes:

- During screening, if QTcF is prolonged on the initial 12-lead ECG (ie, ≥450 msec [males] or ≥470 msec [females]), the average QTcF of three 12-lead ECGs, recorded 4 minutes apart, must not be ≥450 msec for male participants and ≥470 msec for female participants.

- At Visit 2.1 (Day 1), if QTcF is prolonged based on a site-evaluated ECG, a total of three 12-lead ECGs should be obtained at least 4 minutes apart. The average QTcF of the three 12-lead ECGs will be used to determine participant's eligibility.
- During the DB Treatment Phase, if a clinically significant finding is identified in QTcF, the average QTcF of three 12-lead ECGs, recorded 4 minutes apart, will be used to assess QTc stopping criteria (see Section 7.1.2, QTc Stopping Criteria).

During the collection of ECGs and vital signs, participants should be in a quiet setting without distractions (eg, television, cell phones). Participants should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: 12-lead ECG(s), vital signs, blood draw.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and a random urine sample for urinalysis will be collected as noted in Section 10.2. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

Clinical laboratory assessments, including TSH (all participants, at screening only), follicle stimulating hormone (FSH) (female participants only, at screening only if required for documentation that a female participant is not of childbearing potential, see Inclusion Criterion 12), FT_4, hematology, serum chemistry, HbA1c, lipid panel, and urinalysis that should be performed at approximately the same time under fasting conditions, except possibly at the screening visit. The clinical laboratory assessments, ECGs and vital signs should be done first and then food or coffee provided before PROs and clinician-rated observations are carried out.

8.2.5. Pregnancy Testing

For female participants of childbearing potential, a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed as indicated in the SoA (see Section 1.3) to establish absence of pregnancy. Additional serum and urine pregnancy tests may be conducted as needed per the investigator's judgment.

8.2.6. Columbia Suicidality Severity Rating Scale (C-SSRS)

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

8.2.7. Arizona Sexual Experiences Scale (ASEX)

CCI

[redacted]

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

CCI

[redacted]

[redacted]

8.2.9. Mini Mental State Examination (MMSE) - Screening Only

The MMSE test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used in medicine and allied health to screen for dementia. The test is divided into 2 sections: the first section requires vocal responses and covers orientation, memory, and attention. The second part assesses ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a Bender-Gestalt Figure. The score ranges from 0 (minimum score) to 30 (maximum score) and it is calculated by the sum of the sub-items scored 0 (incorrect answer) or 1 (correct answer) (Creavin 2016; Folstein 1975). The MMSE will be done only in participants of age ≥65 years.

8.2.10. Menstrual Cycle Tracking

Menstrual cycle tracking (start date of last menstrual period) will be documented at the study visits specified in the SoA (Section 1.3) only for female participants with a menstrual cycle.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQCs, from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events, including AESIs, will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study. Further details on AEs, SAEs, and PQCs can be found in Section 10.4.

This study allows the use of locally approved (including emergency use-authorized [or country/territory-specific equivalent emergency use approved]) COVID-19 vaccines. All AEs, including those following vaccination, should be included in the source and entered in the eCRF. See Section 10.9, for further details regarding COVID-19.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All AEs, including AESI and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information spontaneously reported by an investigator beyond the time frame specified in the protocol.

Serious Adverse Events

All SAEs occurring during the study must be reported to the appropriate sponsor contact person by study site personnel immediately, but no later than 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

A possible Hy's Law case is defined by the occurrence of ALT/AST ≥3 x ULN, ALP <2 x ULN together with Tbili ≥2 x ULN or international normalized ratio (INR) >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and must be reported as an SAE to the sponsor in an expedited manner, using the SAE form, even before all other possible causes of liver injury have been excluded.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned during the study (see Section 8).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned during the study visits.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE, or product quality complaint (PQC) as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events and the special reporting situation of pregnancy will be followed by the investigator as specified in Section 10.4.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate IEC/IRB that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events:

- Suicidal thinking, ideation, and behavior

- Sleep changes, difficulty sleeping, reduced sleep, abnormal sleep, tiredness, fatigue, and reduced energy
- Difficulty in sexual desire, performance, or satisfaction
- Reduced appetite and weight changes (loss or increase)
- Activation or hypomania/mania
- Irritability, anger, and impulsive behavior
- Agitation, tension, panic attacks, and phobia
- Depression

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries/territories in which the studies are conducted.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using an SAE reporting form. Any participant who becomes pregnant during the study must be promptly discontinued from further study intervention.

Because the effect of the study intervention on sperm is unknown, pregnancies in partners of male participants included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy for female participants who become pregnant, or where the pregnancy was the result of male participant and his partner, and any postnatal sequelae in the infant will be required.

8.3.6. Adverse Events of Special Interest

The following AEs are considered to be of special interest in this study:

- CCI
- CCI

Investigators are instructed to inquire about the occurrence of such events during the collection of AEs at each visit. When reported investigators will be required to complete additional eCRF pages for the AESI. At a minimum, a description of the event (including any known precipitating circumstances), the time relative to dose administration, the duration, concomitant treatment, and outcome of the event will be reported. See Section 10.4.3.1 for guidance on assessing the severity of AESI.

Note: If the event meets the seriousness criteria (see Section 10.4.1), the Serious Adverse Event Form must also be completed according to the SAEs reporting timeline, ie, within 24 hours of having become aware of the event, even if all details are not available (see Section 10.4.5).[a]

8.4. Digital Biomarker Assessments

Objective behavior and physical measurements will only be administered where applicable and/or permitted per local regulations.

Objective behavior and physical measurements, including Speech/Facial Digital Biomarker using a smartphone application software, will be performed as optional assessments. In addition, the RLT will be performed as an objective assessment (as a sub-study) of the ability to modulate behavior as a function of prior reinforcement.

8.4.1. Speech/Facial Digital Biomarker Analysis (Optional)

Studies have supported the view that vocal acoustic properties in speech may serve as digital biomarkers for depression severity and treatment response (Mundt 2007; Mundt 2012). In this study, the MADRS physician-patient interview may be recorded for data quality monitoring. To reduce participant burden, consent will be obtained to use the same speech/video samples for exploratory analysis of acoustic and linguistic properties, and facial emotional characteristics. For the linguistic analysis, the speech sample may also undergo analysis of lexicosyntactic variables for the types of words used and sentence complexity, and analysis of semantic measures to quantify information content. Semantic measures, such as semantic coherence (ie, how well he or she stayed on topic) and syntactic structure (eg, phrase length and use of determiner words that link the phrases) have been associated with the onset of psychosis in high-risk participants (Bedi 2015).

8.4.2. Reward Learning Task (RLT)

The RLT provides an objective assessment of the ability to modulate behavior as a function of prior reinforcement). The RLT is a computerized signal detection task to measure the sensitivity to reward in children with attention deficit hyperactivity disorder (ADHD) (Tripp 1999). It was further contextualized as an objective measure for anhedonia (Pizzagalli 2005).

This task measures the participant's ability to modulate behavior in response to rewards (Pizzagalli 2005). In each trial, the participant is asked to identify which type of image, out of 2 groups of similar images (Group A stimuli and Group B stimuli), is displayed. Critically, the

[a] The intention is to collect PK sample around the time of occurrence of these events (see Section 1.3, SoA).

difference between the 2 sets of images is small and the correct responses of 1 type are followed by rewards 3 times more frequently than correct responses of the other type. The participant is specifically instructed that not all correct responses will be rewarded, and the goal is to maximize reward. One key measure is response bias, a measure of the degree to which the participant preferentially chooses the response that is more frequently rewarded. Other measures include reaction time and discriminability, a measure of the participant's ability to discriminate between the 2 sets of images, learning rate, and reward sensitivity.

8.5. Pharmacokinetics

Plasma samples will be used to evaluate the PK of aticaprant. Plasma collected for PK may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

8.5.1. Evaluations

Venous blood samples of approximately 4 mL for the determination of plasma concentrations of aticaprant and any relevant metabolite(s) (if warranted) will be collected from participants per the SoA (see Section 1.3).

The exact dates and times of PK blood sample collection must be recorded, along with all concomitant medications (dose, drug, start and stop date). Study intervention dosing time on the day before each PK sample collection will be accurately recorded by exact dosing date and time by the participant in the participant diary. In addition, in participants who have ongoing AESI, or AESI related to an SAE leading to discontinuation every effort will be made to collect additional unscheduled PK sample (This blood sample should be collected as close as possible to the AESI or AESI related SAE occurrence, but preferably within 72 hours of the last study intervention administration).

Venous blood samples will be collected for the analysis of aticaprant. Samples collected for analyses of aticaprant plasma concentration may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained. Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

During the DB phase, blood samples for PK will be collected from all participants, including placebo-treated participants, but samples from placebo-treated participants will not be analyzed for PK. These samples will be stored and may be analyzed if needed (eg, suspicion of an incorrect treatment assignment).

8.5.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of aticaprant (and any relevant metabolite(s), if warranted) using a validated, specific, and sensitive liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor.

In addition, plasma PK samples may be stored for future analysis of the metabolite profile.

8.5.3. Pharmacokinetic Parameters and Evaluations

Parameters

Plasma concentration-time data will be displayed by visit date and time for aticaprant.

The plasma concentration-time data of aticaprant will be analyzed using population PK modeling. Typical population values of basic PK parameters (eg, aticaprant clearance, distribution volume) will be estimated together with the inter-individual variability. Effects of participant demographics, laboratory parameter values, and other covariates on the PK of aticaprant will be explored. The results of the population PK analyses will be reported separately.

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between MADRS total score (and possibly selected AEs as additional PD parameters) and PK metrics of aticaprant may be evaluated. If there is any visual trend in graphical analysis, suitable models will be applied to describe the exposure-effect relationships. The results of the exposure-response evaluations will be presented in a separate report.

8.6. Biomarkers

Blood samples will be collected during the DB Treatment Phase: (a) to confirm diagnostic biomarker signatures predictive of enhanced clinical improvement to aticaprant; (b) to explore biomarkers that help to explain interindividual variability in efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of adjunctive aticaprant, or that may be associated with MDD in general and/or specific symptoms, such as anhedonia.

Biomarkers may be added or deleted based on scientific information or technical innovations under the condition that the total volume of blood collected will not be increased.

To avoid interference caused by lipid content in the morning blood specimens collected for biomarker evaluation, biomarker samples will be collected under fasting conditions and prior to study intervention administration.

Menstrual cycle will be tracked in premenopausal female participants who are still having their menses during the study as indicated in the SoA (see Section 1.3).

8.7. Immunogenicity Assessments

Not applicable.

8.8. Pharmacogenomic and Epigenetic (DNA, RNA) Assessments

Participation of pharmacogenomic blood sample collection is optional. Participants must sign a separate ICF if they agree to participate in the optional DNA and RNA sample collection for research (where local regulations permit). Refusal to give consent for the optional DNA and RNA research samples does not exclude a participant from the study.

With participant's consent, blood sample collection per the SoA (see Section 1.3) will be performed to allow for the potential identification of genetic (DNA and RNA), epigenetic factors and transcriptional changes that may influence the efficacy, pharmacokinetics, pharmacodynamics, safety and tolerability of adjunctive aticaprant, or that may be associated with MDD in general and/or specific symptoms, such as anhedonia.

8.9. Participant Medical Information Prior to, During and After the Study (Optional Real-world Data Collection)

Tokenization (US only) enables linkage of clinical trial data with real-world evidence (RWE) data, which allows for the correlation of patient characteristics at baseline with long-term clinical outcomes (eg, psychiatric hospitalization) available from RWE data. For participants who have provided consent for the optional substudies, medical data (electronic health records, claims and laboratory data from other care settings) from 5 years prior to study enrollment until 5 years after study completion may be accessed utilizing tokenization and matching procedures (ie, the generation of anonymous identifiers or "tokens" [hashed and encrypted combinations of identifying elements] to allow linking of participant data from different sources without compromising the participant's confidentiality). Data collection is optional. These data may be used for exploratory analyses to enhance our understanding of the impact of prior medical history on the response to the study intervention on efficacy and duration of efficacy as well as AEs that may occur during and after completion of the study. The analyses will be described in detail in a dedicated analysis plan.

8.10. Ongoing Participant Review

AEs and concomitant medication will be recorded at each visit, including the remote contact visit. The participant will also maintain a diary for current antidepressant use, which will be reviewed by the site at each clinical visit.

8.11. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. 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 2-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.

9.2. 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 enrolled in this study.

Participants entering the DB Treatment Phase will be randomized in a 1:1 ratio to receive adjunctive aticaprant 10 mg or adjunctive placebo. A minimum of 324 adult participants with MDD ANH+ and approximately 106 adult participants with MDD ANH- will be enrolled. Assuming an effect size of 0.4 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 90% power for the comparison between aticaprant 10 mg and 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 0.45 (mean difference between treatment groups of -4.1 and a pooled standard deviation of 8.98) for the change from baseline to Day 43 in MADRS total score for the relevant study population, and clinical judgment. Given that 67953964MDD2001 was a Phase 2 study, the sample size for the primary efficacy analysis for this Phase 3 study was determined using a smaller effect size of 0.4 to allow for greater variability that can be expected for a global study that is larger in scope.

It is expected that approximately 108 elderly participants (65 to 74 years of age, inclusive) will be enrolled 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 will be described in the respective country/territory-specific amendments to the protocol.

9.3. Participant Analysis Sets

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

Analysis Sets	Description
All Participants	All participants who sign the ICF.
Randomized	All participants who were randomized in the study.
Full Analysis Set (FAS_ANH+)	All adult randomized participants with MDD ANH+ who take at least 1 dose of study intervention.
Safety	All randomized participants (adults and elderly) who take at least 1 dose of study intervention.

The analyses of primary and key secondary endpoints will be based on the FAS_ANH+. The analyses of other efficacy endpoints and the corresponding analysis sets will be specified in the Statistical Analysis Plan.

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

9.4. Statistical Analyses

Statistical analysis will be performed by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

The SAP will be finalized prior to the database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

The assessment of primary and secondary (key and other) endpoints will be conducted on the FAS_ANH+, which includes randomized adult (not elderly) participants with MDD ANH+ who took at least 1 dose of study intervention.

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.

Analysis of Data from China and Japan

Data from China and Japan (if participating) will be combined with the global data for local registration in the respective countries/territories. Details about the analysis will be described in respective country/territory-specific amendments to the global protocol.

9.4.2. Efficacy Analysis

9.4.2.1. Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the change from baseline in MADRS total score at Day 43 in FAS_ANH+.

Primary Estimand: This estimand is defined to address the primary objective when the study intervention is taken as directed. This estimand has the following 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 participants (18 to 64 years of age, inclusive) with MDD ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI, as reflected by the inclusion/exclusion criteria.

Endpoint: Change in MADRS total score from baseline to Day 43.

Intercurrent events: The following intercurrent events will be managed using a hypothetical strategy (ie, as if the intercurrent event did not occur):

- Discontinuation of study intervention only,
- Discontinuation of both study intervention and current antidepressant,
- Switch of study intervention only (ie, initiation of another antidepressant after discontinuation of study intervention),
- Switch of current antidepressant therapy only,
- Switch of study intervention and current antidepressant therapy.

Summary measure: Difference in treatment means.

Primary analysis: Change from baseline in MADRS total score will be analyzed by MMRM based on observed case. 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 MADRS total score as a covariate. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. In case of convergence problems, 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. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. Comparison between aticaprant 10 mg and placebo at Day 43 will be performed using the appropriate contrast. Difference in least square means and 2-sided 95% confidence intervals (CI) will be presented.

Sensitivity analysis: Delta adjustment tipping point will be conducted as a sensitivity analysis.

Justification of MMRM: 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). 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. 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 in this Phase 3 study will be MMRM, with sensitivity analysis using the tipping point method to stress test the efficacy findings under MNAR assumption.

Any supplementary estimands that are identified will be described in the SAP.

9.4.3. Secondary Endpoint(s)

Key Secondary Efficacy Endpoint

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

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

Testing Procedure for Primary and Key Secondary Endpoints

A fixed sequence testing procedure will be applied to control the family-wise error rate (FWER) at 2-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 2-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.

Other Secondary and Exploratory Efficacy Endpoints

The definitions and analyses for the other (secondary and exploratory) efficacy endpoints and study populations (adult participants with MDD ANH+, adult participants with MDD ANH-, and all participants MDD ANH+/-) will be described in the SAP. To evaluate the consistency of efficacy in subgroups of participants, the analysis of primary and key secondary endpoints will be performed by intrinsic (baseline demographics) and extrinsic (baseline disease characteristics, medical history, baseline medications, etc) factors.

9.4.4. Safety Analyses

Safety analyses will be based on the safety analysis set, which consists of all randomized participants (adults and elderly) who take at least 1 dose of study intervention.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the MedDRA. All reported treatment-emergent AEs, ie, AEs with onset during the DB Treatment Phase, or AEs that are a consequence of a pre-existing condition that has worsened since baseline, will be included in the analysis. For each treatment-emergent AE, and AESI (see Section 8.3.6), the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study intervention. Serious adverse events (SAEs) will be summarized separately.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe AE or an SAE.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test and study intervention. Markedly abnormal ranges (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point.

The proportion of participants with markedly abnormal results will be presented for each analyte and study intervention group.

A listing of participants with any markedly abnormal laboratory results will also be provided.

Electrocardiogram

The effects on ECG measurements (heart rate, PR interval, QT interval, and QTc interval) will be evaluated using descriptive statistics and frequency tabulations. QTc intervals will be calculated using the Bazett and Fridericia correction methods and summarized accordingly (Bazett 1920).

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point. The percentage of participants with QTc interval higher than pre-specified levels will be summarized, as will the percentage of participants with QTc interval increases from baseline >30 milliseconds or >60 milliseconds.

A listing of participants with abnormal ECG findings will be presented. ECG data will be summarized by each parameter and study intervention group. Proportion of participants with abnormal ECG will be presented.

Vital Signs

Descriptive statistics of pulse, sitting blood pressure (systolic and diastolic), and body temperature for observed values will be provided and changes from baseline will be summarized at each scheduled time point by study intervention group. Changes in body weight and BMI will be summarized descriptively.

Withdrawal Effects

Withdrawal effects based on the PWC-20 will be tabulated by study intervention.

ASEX

Sexual dysfunction (ASEX) data will be summarized descriptively at each scheduled timepoint by treatment group.

C-SSRS

Suicide-related thoughts and behaviors based on the C-SSRS will be tabulated by study intervention.

9.4.5. Other Analyses

9.4.5.1. Benefit-Risk Analyses

Benefit-risk assessment for aticaprant 10 mg versus placebo as adjunctive therapy to an antidepressant (SSRI or SNRI) in participants with MDD with or without moderate-to-severe anhedonia (MDD ANH+ or MDD ANH-, respectively) will be assessed using a structured framework approach. Benefits in the assessment will include endpoints for symptoms of depression (eg, change from baseline to Day 43 in the MADRS total score) and anhedonia (eg, change from baseline to Day 43 in DARS total score). Assessment of risk will include clinically meaningful AEs, including treatment-emergent AEs and AESIs.

The benefit-risk assessment will be evaluated based on the between treatment differences (eg, risk difference or excess number of events) for efficacy and safety endpoints. Kaplan-Meier-Product-Limit estimates may also be used to display and evaluate benefits and risks over time. To compare efficacy and safety endpoints in similar units (proportions to proportions, or rates to rates), endpoints will be assessed as the proportions or rates of participants exhibiting each measure. Benefit-risk results will be depicted with effects tables and with other visual representations (eg, forest plots).

9.4.5.2. Pharmacokinetic Analyses

Blood samples will be collected for determination of plasma concentrations of aticaprant as indicated in the SoA (Section 1.3).

A population-based pharmacokinetic (PK) analysis using PK data from previous studies of aticaprant Phase 1 and Phase 2a studies will be performed and post hoc Bayesian estimates of aticaprant PK parameters will be derived. Available covariates will be included in the model as necessary.

The results of the population PK and PK-PD analysis will be reported separately, as appropriate.

9.4.5.3. Biomarker Analyses

Biomarker Analyses

Laboratory data of biomarker levels at baseline will be analyzed and combined in a multivariate model to confirm a biosignature that will be identified in Study 67953964MDD3001. The details of the analysis will be described in the statistical analysis plan.

Digital Biomarker Analyses

Accuracy, reaction time, and response bias for each block, learning rate, and reward sensitivity will be derived from the data collected from RLT. De-identified speech/video features during

participant interviews may be extracted. Individual features measured at baseline and multivariate models will be assessed for their ability to predict treatment outcome of aticaprant over placebo as measured by change in MADRS from baseline at the end of the DB Treatment Phase. Change of exploratory digital endpoint (for example, response bias from block 1 to block 2 or from block 1 to block 3, learning rate, and reward sensitivity) will also be assessed in the aticaprant arm compared to placebo.

Exploratory analysis correlating RLT metrics, the speech/video features with clinical characteristics of depression symptoms and biomarker measures, and biomarker measures will be performed as well.

9.4.5.4. Immunogenicity Analyses

Not applicable.

9.4.5.5. Exploratory Biomarker Analyses

The exploratory RNA, serum, plasma biomarkers will be tabulated by treatment and summary statistics will be calculated. Post-treatment changes in exploratory biomarkers will be summarized by treatment group. Associations between baseline biomarker levels and clinical endpoints, such as change in MADRS, may be explored. Results may be presented in a separate Biomarker Report.

9.4.5.6. Pharmacokinetic/Pharmacodynamic Analyses

A population-based PK analysis using PK data from previous studies of aticaprant Phase 1 and Phase 2a studies will be performed and post hoc Bayesian estimates of aticaprant PK parameters will be derived. Available covariates will be included in the model as necessary.

The relationship between MADRS total score (and possibly selected AEs) and PK metrics of aticaprant may be evaluated. Based on any visual trend in graphical analysis, suitable models will be applied to describe the PK/PD relationships between PK and efficacy or safety.

The results of the both the population PK and PK-PD analyses will be performed and reported separately, as appropriate.

9.4.5.7. Pharmacogenomic Analyses

A composite genotype may be derived from the raw genotyping data for the analyzed genes, as appropriate. Specific analyses will include, but are not limited to, interrogation of single nucleotide polymorphisms in whole blood DNA at discrete loci implicated in mood. The relationship between genetic subgroups and pharmacokinetic endpoints may be examined through descriptive statistics or graphically. Transcriptional changes may be analyzed in correlation to clinical outcomes.

DNA and RNA samples will be used for research related to aticaprant and depression. They may also be used to develop tests/assays related to aticaprant. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome (as appropriate) in relation to aticaprant or clinical endpoints.

Results will be presented in a separate report.

9.5. Interim Analysis

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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

ABV	alcohol-by-volume
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANH+	with moderate-to-severe anhedonia
ANH-	without moderate-to-severe anhedonia
AP	alkaline phosphatase
API	active pharmaceutical ingredient
ASEX	Arizona Sexual Experiences Scale
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
CGI-S	Clinical Global Impression - Severity
CI	confidence interval
COA	clinical outcome assessment (paper or electronic as appropriate for this study)
CRF	case report form(s) (paper or electronic as appropriate for this study)
C-SSRS	Columbia Suicidality Severity Rating Scale
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DARS	Dimensional Anhedonia Rating Scale
DB	double-blind
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th edition
DOR	delta opioid receptor
ECG	electrocardiogram
eDC	electronic data capture
EOT	end-of-treatment
EQ-5D-5L	EuroQol-5 Dimension-5 Level
EQ-VAS	EQ visual analogue scale
EW	Early Withdrawal
FAS	full analysis set
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
FT_4	free thyroxine
GAD-7	Generalized Anxiety Disorder 7-item Scale
GCP	Good Clinical Practice
HbA1c	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HDRS-17	17-item Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IDFU	Investigational directions for use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IWRS	interactive web response system
KOR	kappa opioid receptor

LC-MS/MS	liquid chromatography/mass spectrometry/mass spectrometry
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD	major depressive disorder
MDD ANH+	MDD with moderate-to-severe anhedonia (ANH+)
MDD ANH-	MDD without moderate-to-severe anhedonia (ANH-)
MedDRA	Medical Dictionary for Regulatory Activities
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MMRM	mixed model for repeated measures
MMSE	Mini Mental State Examination
MOR	mu opioid receptor
NIMP	Non-Investigational Medicinal Product
PCP	phencyclidine
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire, 9-item
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	Patient-Reported Outcome(s) (paper or electronic as appropriate for this study)
PROMIS	Patient-Reported Outcomes Measurement Information System
PROMIS-APS 8a	PROMIS Short Form v2.0 - Ability to Participate in Social Roles and Activities - 8a
PWC-20	Physician Withdrawal Checklist 20-items
QLDS	Quality of Life in Depression Scale
QTc	Corrected QT
QTcF	Corrected QT interval by Fridericia
RLT	Reward Learning Task
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID-CT	Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version
SHAPS	Snaith-Hamilton Pleasure Scale
SIGH-D	Structured Interview Guide for the Hamilton Depression Scale
SIGMA	Structured Interview Guide for the MADRS
SIQA	Site Independent Qualification Assessment
SNRI	serotonin-norepinephrine reuptake inhibitor
SoA	Schedule of Activities
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum drug concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WHO	World Health Organization

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a CRF as determined by the protocol. Data in this system may be considered source documentation
PRO	A measurement based on a report that comes directly from the patient about the status of the patient's health condition without interpretation of the patient's response by a clinician or anyone else

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol-required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.

Note: An optional/ad-hoc assessment of INR will be performed by the central laboratory in case of liver function parameters elevation.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose (in fasting condition when possible)
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)</td><td>Total bilirubin and Direct bilirubin
Alkaline phosphatase (AP)
Creatine phosphokinase (CPK)
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol
• Total cholesterol
• LDL-cholesterol
• HDL-cholesterol
Triglycerides
Magnesium</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.6.

ALT or AST elevations >5 x ULN at least twice over a 2-week period.

A possible Hy's law Case is defined by the occurrence of ALT/AST ≥3 x ULN, ALP <2 x ULN together with Tbili ≥2 x ULN or INR >1.5 (if measured).</td></tr>
</table>

<table>
<tr><td rowspan="2">Routine Urinalysis</td><td><u>Dipstick</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Sediment (if initial result is abnormal)</u>
Red blood cells
White blood cells
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td colspan="2">If initial result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the initial results and the flow cytometric results, the sediment will be examined microscopically.</td></tr>
<tr><td>Other Tests (at Screening, Baseline, or During Treatment)</td><td colspan="2">• Serum or Urine Pregnancy Testing for female participants of childbearing potential only.

Note: a serum pregnancy test must be performed at screening, and urine pregnancy tests must be performed as indicated in the SoA to establish absence of pregnancy. Additional serum and urine pregnancy tests may be conducted as needed per the investigator’s judgment.

• Urine drug test for drugs of abuse (eg, opiates [including methadone], cocaine, amphetamines, methamphetamines, cannabinoids, cannabidiol [CBD], phencyclidine [PCP], barbiturates, or 3,4-methylenedioxymethamphetamine [MDMA]). Urine drug tests will be done by the site at screening, at baseline, and as needed per the investigator's judgment.

• In some countries, a urine or blood sample may be collected as an optional way to assess compliance with current antidepressant medications.

• Thyroid-stimulating hormone (TSH) (screening only) for any participant (regardless of thyroid history), if the TSH value is out of range or for participants with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening, a free thyroxine (FT_4) will be conducted. If the FT_4 value is abnormal and considered to be clinically significant (after discussion with the study responsible physician/scientist or designee) the participant is not eligible. For participants with abnormal TSH or taking thyroid medication, FT_4 should be performed whenever the TSH is performed.

• Follicle stimulating hormone (FSH) (female participants only, at screening only if required for documentation that a female participant is not of childbearing potential, see Inclusion Criterion 12).

• Hemoglobin A1c (HbA1c).

• Alcohol breath test (at screening, at baseline, and as needed per the investigator's judgment).</td></tr>
</table>

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and country/territory-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

In situations where a departure from the protocol is unavoidable during the study, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact must be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree

on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated Clinical Trial Agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all sub-investigators.
- Documentation of sub-investigator qualifications (eg, curriculum vitae).
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the Independent Ethics Committee or Institutional Review Board (IEC/IRB) with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.3.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.3.

10.3.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant must give consent according to local requirements after the nature of the study has been fully explained. Study sites may be asked by the sponsor to obtain informed consent using a validated electronic system instead of a paper-based process. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent must be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent must be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

10.3.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate

technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/territories.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete or make requests concerning his or her personal data in accordance with applicable data protection law. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

In the event of a data security breach, the sponsor will apply measures to adequately manage and mitigate possible adverse effects taking into consideration the nature of the data security breach as necessary to address other obligations such as notifying appropriate authorities in accordance with applicable data protection law.

Exploratory biomarker and PK research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.3.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. The start of the storage period is defined as the completion date of the clinical study report (CSR). Samples will only be used to understand depression and disorders with depressive symptoms, and/or the use of aticaprant as adjunctive therapy, to understand differential intervention responders, and to develop tests/assays related to aticaprant. The research may begin at any time during the study or during the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1).

10.3.6. Committees Structure

An IDMC will be commissioned for this study to periodically review safety data. The IDMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

10.3.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding aticaprant or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish the goals of this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of aticaprant, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in the publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will

not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, and periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor may review the electronic CRF (eCRF) for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with other data sources.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in the eCRF. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Data must be entered into the eCRF in English. The eCRF must be completed as soon as possible after a participant visit and the forms must be available for review at the next scheduled monitoring visit.

All participative measurements (eg, pain scale information or other questionnaires) will be completed by the same individual who made the initial baseline determinations whenever possible.

If necessary, queries will be generated in the eDC tool. If corrections to an eCRF are needed after the initial entry into the eCRF, this can be done in either of the following ways:

- Investigator and study site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study site personnel.

10.3.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents must be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by study participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the eCRF and will be considered source data:

- Race
- History of all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum, etc
- Blood pressure and pulse/heart rate
- Height and weight

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic (eSource) system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. These data are electronically extracted for use by the sponsor. If eSource is utilized, references made to the eCRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the eCRF. Data in this system may be considered source documentation. Centralized and/or remote data will be identified as source from the vendor and the collected information used (eg, questionnaires, scales, or other tools) will be considered as source and maintained centrally by the vendor(s). In these cases, original entries will be made electronically via a tablet or other device. The data (ie, clinical study-specific data fields as determined by the protocol) will not be maintained in a hospital or clinic record as source documentation. The site's data will be made available to the site via a portal for review and will also be provided as a final data transfer at the end of the study.

10.3.11. Monitoring

The sponsor will use a combination of monitoring techniques, including central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study site personnel. The sponsor expects that, during monitoring visits, the relevant study site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will

meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study site personnel will be available to provide an update on the progress of the study at the site.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study site personnel are responsible for being present and available for consultation during routinely scheduled study site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator must immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.3.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP E6 (Section 8 Essential Documents for the Conduct of a Clinical Trial) and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.3.14. Study and Site Start and Closure

First Act of Recruitment

The first participant screened is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

An AE is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation [ICH]).

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

Serious Adverse Event

An SAE based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

  *Medical and scientific judgment must be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected AE occurs for which there is evidence suggesting a causal relationship between the study intervention and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For aticaprant, the expectedness of an AE will be determined by whether or not it is listed in the IB. For background selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) treatment that is required to be continued along with the study intervention and with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the applicable product information sheet (eg, package insert/summary of product characteristics).

10.4.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is assessed by the Investigator. The following selection must be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term “reasonable causal relationship” means there is evidence to support a causal relationship.

10.4.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator must use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.3.1. Guidance for Assessing Severity of Adverse Events of Special Interest

The following guidance is provided as recommendation to consider when assessing the severity of CCI in the aticaprant studies:

CCI

[redacted]

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention

- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breastfeeding
- Reporting of participant pregnancy or participant partner(s) pregnancy

Special reporting situations must be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the eCRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All SAEs that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes

- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as an SAE, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or AE (eg, social reasons such as pending placement in long-term care facility).
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

The cause of death of a participant in a study within 30 days of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered an SAE.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.4.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Procedures

All initial PQCs must be reported to the sponsor by the study site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who must be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5 Pregnancy and Section 10.4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Female Participant of Childbearing Potential

A female participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Female Participant Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in female participants on HRT, the female participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  - Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.
  - Has congenital abnormalities resulting in sterility.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active), a female participant must begin a highly effective method of contraception, as described throughout the Inclusion Criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by male participants or female participants must be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED FOR MALE OR FEMALE PARTICIPANTS DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception must be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation –oral –intravaginal –transdermal –injectable
Progestogen-only hormone contraception associated with inhibition of ovulation –oral –injectable
Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
Male or female condom with or without spermicide[b]
Cap, diaphragm, or sponge with spermicide
A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[b]
Periodic abstinence (calendar, symptothermal, post-ovulation methods)
Withdrawal (coitus-interruptus)
Spermicides alone
Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use must be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Male condom and female condom must not be used together (due to risk of failure with friction).

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

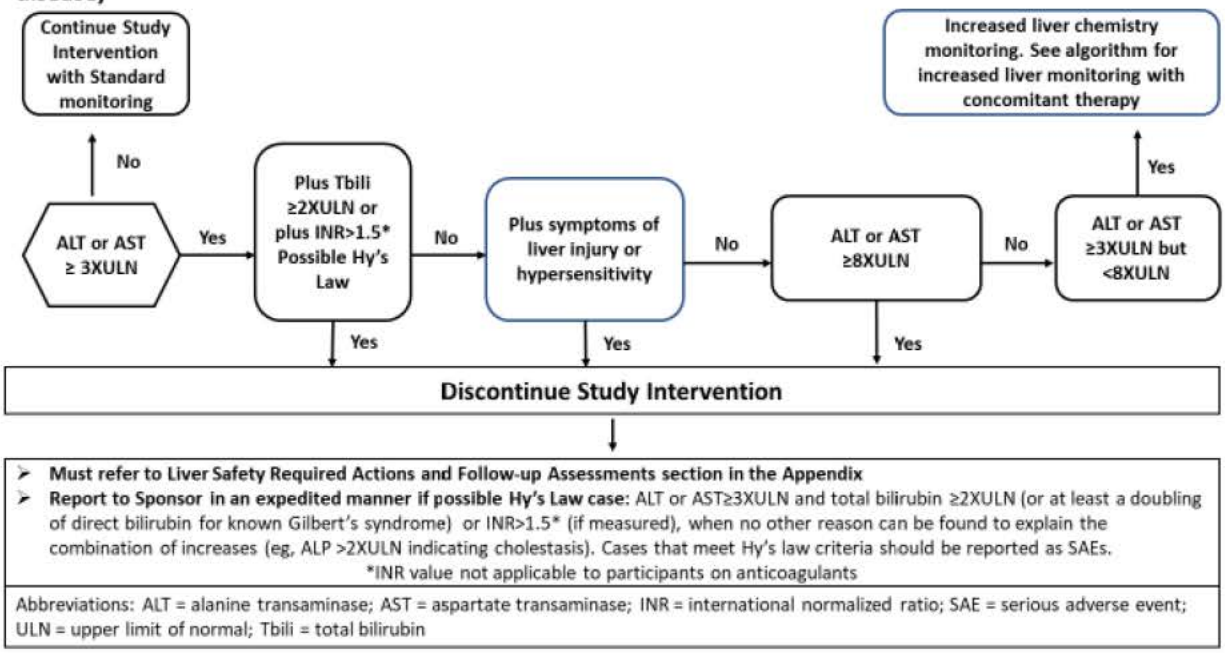
10.6.1. Stopping Algorithm

10.6.1.1. ALT or AST

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Guideline Algorithm for Monitoring, Assessment & Evaluation of Abnormal Liver Tests in Participants with no Underlying Liver Disease and normal baseline ALT, AST, Alkaline Phosphatase and Bilirubin

Phase 3-4 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)



The following definition of patterns of drug-induced liver injury (DILI) is used when directing the work-up for potential DILI based on elevations of common liver tests (LT):

Histopathology	LT	Ratio (ALT/ULN)/(AP/ULN)
Hepatocellular	**ALT ≥3 x ULN**	**≥5**
Cholestatic	**ALT ≥3 x ULN**	**≥2**
Mixed	**ALT ≥3 x ULN and AP ≥2 x ULN**	**>2 to <5**

1. Obtain detailed history of present illness (abnormal LTs) including (if not already obtained at baseline) height, weight, BMI. Assess for abdominal pain, nausea, vomiting, scleral icterus, jaundice, dark urine, pruritus, rash, fever, and lymphadenopathy. Assess for history of prior abnormal liver tests, liver disease including viral hepatitis, obesity, metabolic syndrome, congestive heart failure (CHF), occupational exposure to hepatotoxins, diabetes mellitus (DM), gallstone disease or family history of gallstone or liver disease. Specifically record

history of alcohol use, other meds including acetaminophen, NSAID, over-the-counter (OTC) herbal supplements, vitamins, nutritional supplements, traditional medicines, and street drugs; and document whether or not there has been any recent change in any other prescription drugs and start-stop dates.

2. Obtain travel history to endemic areas for hepatitis A, hepatitis E. Ask for history of any prior blood transfusions and when they were performed. Perform physical examination, obtain vital signs and BMI, and document presence or absence of scleral icterus, palpable liver including size, degree of firmness or tenderness, palpable spleen including size, ascites, and stigmata of chronic liver disease (spider angiomata, gynecomastia, palmar erythema, testicular atrophy). Allow free text in eCRF for other relevant history and physical information.

Mandatory liver ultrasound with consideration of further imaging (eg, computerized tomography [CT], magnetic resonance imaging [MRI], magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography [ERCP], Doppler studies of hepatic vessels, etc, if indicated based on ultrasound findings or clinical situation). If total bilirubin (Tbili) is >2 x ULN, request fractionation to document the fraction that is direct bilirubin and to rule out indirect hyperbilirubinemia indicative of Gilbert's syndrome, hemolysis or other causes of indirect hyperbilirubinemia. Complete blood count (CBC) with WBC and eosinophil count platelet count, international normalized ratio (INR), and total protein and albumin (compute globulin fraction) should also be documented. If INR is abnormal, prothrombin time (PT), partial thromboplastin time (PTT) should be obtained and these values should be followed until normal, along with documentation of whether parenteral vitamin K was given along with the effect of such treatment on INR. If initial liver function tests (LFTs) and ultrasound do not suggest Gilbert's syndrome, biliary tract disease or obstruction, viral hepatitis serology should be obtained including anti-hepatitis A virus immunoglobin M (anti-HAV IgM), anti-HAV total, HbsAg, anti-HBs, anti-HB core total, anti-HB core IgM, anti-HCV, anti-hepatitis E virus IgM (anti-HEV IgM) (even if has not traveled to an endemic area for hepatitis E), Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) screen.

- If participant is immunosuppressed, test for HCV RNA and HEV RNA.
- If HbsAg or anti-HB core IgM or anti-HB core IgG positive, also get HBV DNA to detect active HepB, especially in participants who are immunosuppressed.
- If all other hepatitis B serologic tests are negative and anti-HBc total is the only positive test, HBV DNA should be obtained to detect reactivation of hepatitis B.

Assuming that the history, physical, and initial imaging and laboratory has not revealed a cause of elevated LTs, screen for other causes of liver disease including: Total protein and albumin (estimate globulin fraction and obtain quantitative immunoglobulins if elevated), antinuclear antibody (ANA), anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-liver-kidney microsomal antibodies (anti-LKM antibodies), anti-smooth muscle antibodies (ASMA), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). If the pattern of laboratory abnormalities is not hepatocellular, but cholestatic or a mixed pattern (see definitions in table above), then GGT, anti-mitochondrial antibody (AMA) and anti-neutrophil cytoplasmic antibody (pANCA) should also be tested. If there is an indication by history or elevated baseline LTs that there may be an underlying chronic liver disease possibly exacerbated by exposure to the study

intervention in the clinical trial or making the participant more susceptible to DILI, test iron/Total iron binding capacity (TIBC) and ferritin (hemochromatosis), and alpha-1-antitrypsin level. If participant is sick enough to be hospitalized and is under 50 years of age, a slit lamp examination to detect Kayser-Fleischer rings and a 24-hour urine collection for copper should be measured. Consider serum ethanol and/or acetaminophen level and urine drug tests as clinically appropriate.

A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated.

A liver biopsy may be considered:

- if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent.
- if peak ALT level has not fallen by >50% at 30-60 days after onset in cases of hepatocellular DILI, or if peak AP has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent.
- in cases of DILI where continued use or re-exposure to the implicated agent is expected.
- if liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI.

If pertinent, copies of hospital discharge summary, radiology, pathology and autopsy reports should be obtained.

10.6.2. Follow-up Assessments

10.6.2.1. Phase 3-4 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT or AST- ≥5 x ULN and <8 x ULN **and** total bilirubin <2 x ULN or INR<1.5 **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks OR ALT or AST- ≥ 3x ULN and <5 x ULN **and** total bilirubin <2 x ULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the sponsor **within 24 hours** of learning of the abnormality to discuss participant safety • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize, or return to baseline • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 10.6.1. • If ALT or AST- decreases from ALT or AST- ≥5 x ULN and <8 x ULN to ≥3 x ULN but <5 x ULN, continue to monitor liver chemistries weekly • If, after 4 weeks of monitoring, ALT or AST- <3 x ULN and total bilirubin <2 x ULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline

10.7. Appendix 7: Prohibited Concomitant Therapies

This list of medications is not all-inclusive; if necessary, please contact the sponsor's medical monitor for any questions regarding a medication(s).

Please refer to the local prescribing information of the participant's non-study medications for information regarding prohibited concomitant medications. Except where specifically noted, the prohibited medications listed in the following table are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of study intervention until after the last dose of study intervention.

Of note, for any concomitant medication that is not listed below but has the potential to be a strong CYP3A4 inhibitor or inducer or dual moderate CYP3A4/2C9 inhibitor/inducer or coadministration of moderate CYP3A4 inhibitor and moderate CYP2C9 inhibitor, please check with the sponsor's medical monitor.

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
Attention deficit hyperactivity disorder (ADHD) medications (eg, atomoxetine, guanfacine)	N	N	See also "Psychostimulants" row.	Potential PD interaction
Agomelatine	N	N		Potential PD interaction
Amantadine	N	N		Potential PD interaction
Amitifadine	N	N		Potential PD interaction
Antibiotics: Macrolides	N	N		PK - 3A4 inhibitor
Antibiotics: Nafcillin	N	N		PK - 3A4 inhibitor, (2C9 inducer)
Antibiotics: Quinolones	N	N		PK - 3A4 inhibitor
Anorexiants (eg, phentermine, phendimetrazine)	N	N		Potential PD interaction
Anticholinesterase Inhibitors	N	N		Participant population is excluded
Anticonvulsants	N	Y	- Participants with uncontrolled (current or past 6 months) seizures are excluded. - Anticonvulsants with strong CYP3A4 and/or CYP2C9 induction potential (eg, carbamazepine, phenytoin) are excluded. Others with 3A4 and 2C9 inhibition potential, consult with medical monitor before use.	Potential PD interaction PK - 3A4 and 2C9 induction

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
			- Use as adjunctive treatment for major depressive disorder (MDD) is prohibited.	
Antidepressants and medications used for treatment of depression (*other than the specific antidepressant monotherapies listed in inclusion criteria of the protocol*)	N	N	- Only one of the oral antidepressant treatment options listed in Section Inclusion Criteria is permitted. - If a participant is taking a monoamine oxidase inhibitor (MAOI) during the Screening Phase, there must be a minimum washout interval of 2 weeks prior to the first dose of study intervention. - Even if used for other indications (eg, trazodone for sleep), the use of any medication (except the SSRI/SNRI options listed in protocol) is not permitted during the treatment phase.	Potential PD interaction
Antifungals	N	N	Topical antifungals (like terbinafine) are allowed on a case-by-case assessment in consultation with sponsor's medical monitor.	PK - 2C9, 3A4 inhibitors
Antipsychotics	N	N		Potential PD interaction
Antivirals: non-nucleoside reverse transcriptase inhibitor (NNRTI)	N	N		PK - 3A4, 2C9 inducer
Antivirals: Protease Inhibitors	N	N		PK - 3A4 inhibitor
Appetite Suppressants	Y	N		Potential PD interaction
Aprepitant	N	N		PK - 3A4 inhibitor, 2C9 inducer
Avasimibe	N	N		PK - 3A4 inducer, 2C9 inhibitor
Barbiturates	N	N		Potential PD interaction, potential for 2C9/3A4 induction
Benzodiazepines (at dosages equal to or less than the equivalent of 4 mg/day lorazepam) and non-benzodiazepine	Y	Y	Prohibited within 12 hours prior to RLT completion	Potential PD interaction

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
sleeping medication (including zolpidem, zaleplon, eszopiclone, and ramelteon)				
Benztropine	Y	N		Potential PD interaction
Bosentan	N	N		PK - 3A4 & 2C9 inducer
Buspirone	N	N		Potential PD interaction
Chloral hydrate, melatonin, valerian	N	N		Potential PD interaction
Clonidine	N	Y	Continuous use for blood pressure control is allowed.	Potential PD interaction
Conivaptan	N	N		PK - 3A4 inhibitor
Corticosteroids	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are allowed. Intermittent IM/IV corticosteroids are permitted (chronic use prohibited). Episodic or continuous oral use can be discussed on a case-by-case basis with sponsor's medical monitor.	PK - 3A4 & 2C9 inducer
Crizotinib	N	N		PK - 3A4 inhibitor
Dopamine Receptor Agonists (not listed elsewhere)	N	N		Potential PD interaction
Dextromethorphan	N	N	Episodic use can be discussed on a case-by-case basis with sponsor's medical monitor.	Potential PD interaction
Glutamatergic Agents (ketamine, esketamine)	N	N	Episodic use (eg, anesthesia) can be discussed on a case-by-case basis with sponsor's medical monitor.	Potential PD interaction
Imatinib	N	N		PK - 3A4 & 2C9 inhibitor
Methyldopa	N	N		PD interaction
Metyrosine	N	N		Potential PD Interaction
Memantine	N	N		Potential PD interaction
Monoamino-oxydase inhibitors (MAOIs)	N	N		Potential PD interaction
Mood Stabilizing Agents (eg, lithium)	N	N		Potential PD interaction
Norepinephrine and dopamine reuptake inhibitors (eg, bupropion)	N	N		Potential PD interaction
Opioids	N	N	With sponsor approval, brief treatment with opiates	Potential PD interaction

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
			may be allowed for treatment of acute injuries, etc.	
Opioid Receptor Agonists or Antagonists	N	N		Potential PD interaction
Psychostimulants (eg, amphetamines, methylphenidate, modafinil, armodafinil)	N	N		Potential PD interaction PK - modafinil 3A4 inducer
Psychedelics	N	N		Potential PD interaction
Reserpine	N	N		Potential PD interaction
Scopolamine	N	N		Potential PD interaction
St. John's Wort	N	N		PK - 3A4 inducer Potential PD interaction
Thyroxine/ triiodothyronine (T3), thyroid hormone prescribed for depression	N	N		Potential PD interaction
Thyroid hormone supplement for treatment of thyroid condition only (not for depression)	N	Y	Participants needing supplements must be on a stable thyroid supplement dose for at least 3 months prior to start of the treatment phase.	Potential PD interaction
Trazodone	N	N	Not allowed even if used for other indications (eg, for sleep)	Potential PD interaction

Abbreviations: ADHD: attention deficit hyperactivity disorder; IM: intramuscular; IV: intravenous; MAOI: monoamine oxidase inhibitor; N: Prohibited; NNRTI: non-nucleoside reverse transcriptase inhibitor; PD: pharmacodynamics; PK: pharmacokinetics; PO: oral; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; T3: triiodothyronine; Y: Permitted, with restrictions (please refer to the column labeled "Comments" for additional guidance or contact medical monitor).

Note: Herbal agents or supplements used for the treatment of depression should be discontinued as well unless agreed for continuation by sponsor's medical monitor.

10.8. Appendix 8: Administration of a Patient-Reported Outcome (PRO) at Scheduled Visits

The following guidance will be followed to administer a PRO:

- Provide a quiet, semi-private location for the participant to complete the PROs.
- Ensure participants have access to study staff for questions.
- Instruct participants to complete paper PRO assessments using a blue or black ballpoint pen.
- Explain that all of the information on the PRO assessment(s) is confidential, and that someone from the study staff will only check for completeness and not share the results with other clinical staff.
- Explain to participants the reasons why they are being asked to complete the PRO assessment(s), ie, they are part of the overall medical assessment and are designed to find out more information about how having their disease has affected their life.
- Allow as much time as the participant needs to orient themselves and complete all PRO assessments.
- Instruct the participants to:
  - Read the instructions for each questionnaire carefully.
  - Note the recall period for each questionnaire.
  - Complete all PROs.
- Instruct the participant not to skip any questions/or questionnaires.
- Participants must interpret questions and complete the PRO assessment(s) without help from anyone. If asked for help interpreting or completing the PRO assessment by the participant, please simply reply that there are no right or wrong answers and he/she should use his/her best judgment to complete each question (based on what the participant thinks the question is asking).
- Do not attempt to interpret or explain the instructions, questions, or response options.
- If the participant has difficulty choosing between 2 response options, simply state “choose the answer that most closely matches your experience.”

10.9. Appendix 9: Study Conduct During a Natural Disaster/Major Disruption/ Pandemic

10.9.1. Guidance on Study Conduct During the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Re-consenting of participants will be performed (including remote consenting by phone or video consultation) as applicable for the measures taken and according to local guidance for informed consent applicable during the COVID-19 pandemic.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the Clinical Study Report.

10.9.2. Guidance Specific to this Protocol

These provisions are meant to minimize the risk of exposure to COVID-19 and to safely maintain participants on study intervention while site capabilities are compromised by COVID-19-related restrictions. As restrictions are lifted and the acute phase of the COVID-19 pandemic resolves, sites should revert to original protocol conduct as soon as feasible.

At each contact, participants will be interviewed to collect safety data. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Evaluate the participant's situation on a case-by-case basis and contact the study responsible physician for discussion and decision if necessary. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures.

- The safety of study participants is priority; investigators may make the decision to provide other available therapy to participants in the study. Please discuss any decision to provide other therapy outside of the protocol with the study responsible physician and ensure that this is recorded in the source document and the CRF along with the reason for administration.

Reminder: If a scheduled dose is missed, participants are advised not to administer 2 doses at a time the next day. Dosing should resume the next day. Information about the missing dose should be recorded in participant diaries and in the eCRF study intervention log.

Discontinuations of study intervention and withdrawal from the study due to COVID-19 AEs/SAEs should be documented as discontinuation due to AE. If a participant dies due to COVID-19, "death" should be selected as the reason for treatment discontinuation. Discontinuations for other COVID-19 reasons should be documented with the prefix "COVID-19-related" in the CRF.

Screening Phase

The following recommendations apply to those sites within countries/territories where there is a high localized rate of COVID-19 infection:

Screening of new participants should be postponed until the rate of COVID-19 infection is reduced and under control.

Due to uncertainty around the ability to conduct on-site clinical visits, participants that are currently in screening should be screen failed and clinical standard-of-care for the treatment of depression should be arranged by the study investigator and/or the participant's treating physician. The decision to continue with the participant's current oral antidepressant treatment regimen should be at the discretion of the investigator.

The sponsor will evaluate and approve/reject requests to rescreen an individual participant on a case-by-case basis after the COVID-19 infection is under control.

Study Intervention

In the event that it is not feasible for the participant to be assessed and receive study intervention at the study site (eg, due to temporary site closure), study intervention may be delivered to the participant's home. If this is not feasible the participant may discontinue after consultation with the sponsor's medical monitor.

Study-related Procedures

- 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.
- Missed/ out of window visits or individual assessments should be documented with "COVID-19-related" in the comment section of the CRF.
- It is recommended that close contact be maintained with study participants and remote contact arranged consistent with the participant's regularly scheduled visit interval.

In the event that participants who show worsening, the investigator should contact the sponsor's medical monitor to discuss the best course of action.

Laboratory Assessments

- If laboratory samples cannot be collected by Covance/central laboratory, sample collection and analysis can be performed using the site's local laboratory at the discretion of the investigator. Local laboratory results will not be collected in the electronic data capture (eDC). Only abnormal laboratory values should be reported as (S)AEs.
- If the investigator does not feel laboratory assessments are required at this time, and participant(s) want to avoid any risk to COVID-19 exposure, this rationale should be documented in the source documents.

Exposure to COVID-19

- If a participant develops COVID-19 infection (or suspected) during the Screening Phase, DB Treatment Phase or Follow-up Phase the investigator should contact the sponsor's medical monitor to discuss the best course of action based on individual symptoms/ patient setting and risk-benefit relationship.
- If a participant develops COVID-19 infection (or suspected) during the follow-up period, the investigator should contact the sponsor's medical monitor and assessments should be completed remotely.

Data Collection

- For clinician-completed (MADRS, C-SSRS, CGI-S)[a] scale assessments conducted by a telephone or video contact, the data should be entered directly onto the paper assessment. Ensure that the correct date is present on the assessment form in the eCRF.
- For patient-completed assessments, the DARS, PGI-S anhedonia, PHQ-9, and PGI-S depression should be prioritized and collected via the eCOA device.
- Missed doses should be documented in the CRF in accordance with the CRF completion guidelines.
- For missed doses, enter a logline with 0 as number of tablets taken to document the missed dose and a "COVID-19 related" comment entered on the Comments form.
- All COVID-19-related deviations from the main study protocol will be documented according to the CRF completion guidelines.
- A mitigation plan has been created to address the impact of the COVID-19 global pandemic on the completion of in-person COA assessments.

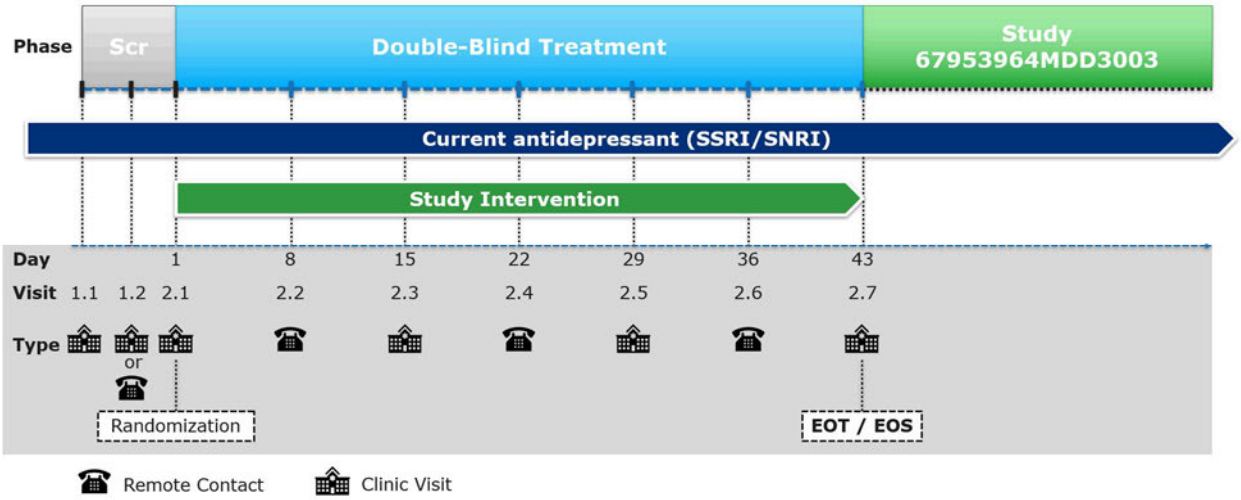
Statistical Analysis

The sponsor will evaluate the totality of the impact of COVID-19 on collection of key study data, and additional data analyses will be outlined in the Statistical Analysis Plan.

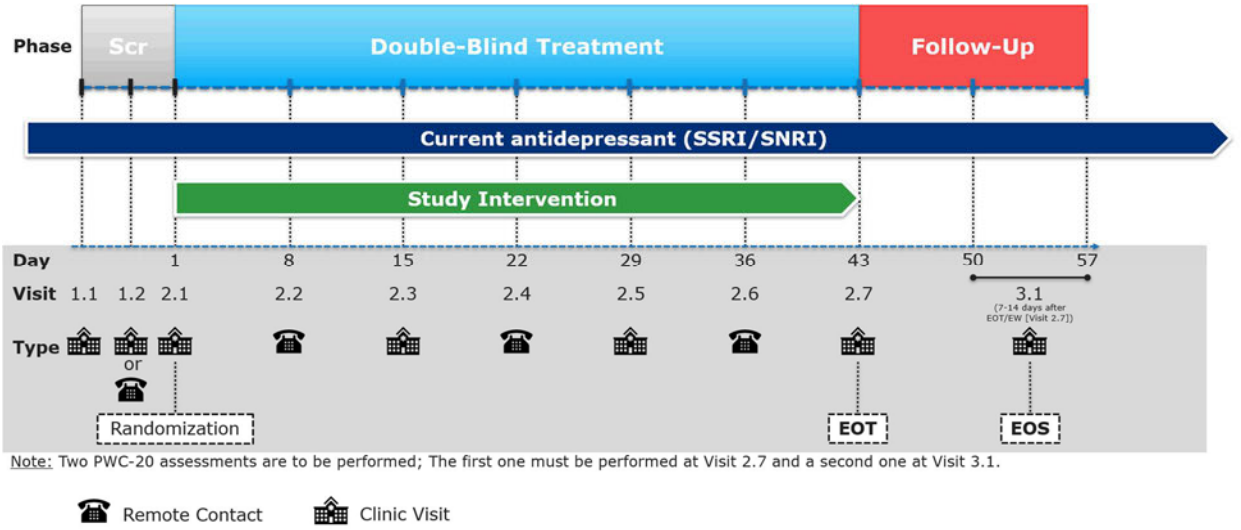
[a] C-SSRS=Columbia Suicide Severity Rating Scale; CGI-S=Clinical Global Impression - Severity; DARS=Dimensional Anhedonia Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale; PGI-S=Patient Global Impression of Severity; PHQ-9=Patient Health Questionnaire, 9-Item.

10.10. Appendix 10: Study Design

Completer continuing in 67953964MDD3003

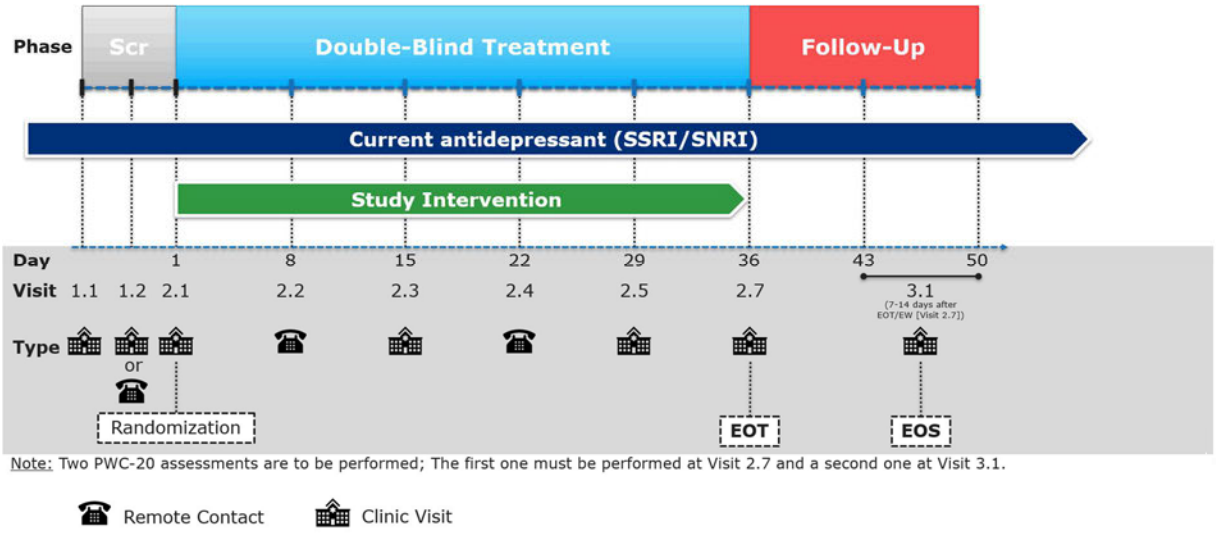


Completer <u>not</u> continuing in 67953964MDD3003



<u>Note:</u> Two PWC-20 assessments are to be performed; The first one must be performed at Visit 2.7 and a second one at Visit 3.1.

Premature discontinuation



Abbreviations: EOS=End of Study, EOT=End of Treatment, EW=Early Withdrawal, SCR=Screening, SNRI=serotonin-norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor

10.11. Appendix 11: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

11. REFERENCES

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INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD MD

Institution: Janssen Research & Development

Signature: electronic signature appended at the end of the protocol Date: _____

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

Signature

User	Date	Reason
PPD	22-Feb-2023 13:28:01 (GMT)	Document Approval