Janssen Research & Development *

Clinical Protocol

Protocol Title

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

VENTURA-7

Short Title

A Study of Oral Aticaprant Versus Placebo to Evaluate the Efficacy and Safety of Aticaprant in Patients with Major Depressive Disorder Who Experience Moderate-to-Severe Loss of Interest and Pleasure as Part of Their Depressive Episode and an Open-labeled Long-term Extension Treatment with Aticaprant

Protocol 67953964MDD3007; 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).

Studies conducted at sites in the European Economic Area (EEA) will be conducted under Regulation [EU] No 536/2014.

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

Confidentiality Statement

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Country/Territory Affected**	**Date**
Amendment 1	All	19 June 2024
Original Protocol	All	02 March 2024

Amendment 1 (19 June 2024)

Overall Rationale for the Amendment: The primary reason for this amendment is to add clinical laboratory measures at certain open label treatment phase visits.

The changes made to the clinical protocol 67953964MDD3007 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
1.3 Schedule of Activities (SoA)	Added clinical laboratory measures during the Open-Label Treatment Phase at Weeks 15 and 23.	Added footnotes g and h to the open label Schedule of Activities.
	Added footnote c describing that Visit 1.2 can be skipped if the lipid panel was previously done.	Provided clarification that Visit 1.2 can be skipped if there is no need for fasting lipids.
	Added footnote p to all efficacy assessments and weight in the Schedule of Activities During the Screening and Double-Blind Treatment Phase.	Added language to clarify that all efficacy assessments and weight must be performed before randomization in the Double-Blind Treatment Phase.
	Added footnote q to the SIQA in the Schedule of Activities During the Screening and Double-Blind Treatment Phase.	Footnote p was previously unattached to the Schedule of Activities.
	Added reference to Section 8 for the recommended order of study assessments.	Added to clarify the recommended order of study assessments at different visits.
	Added footnotes g and h to the Schedule of Activities During the Open-Label Treatment Phase.	Added for consistency with double-blind Schedule of Activities footnotes.
	Removed footnote "Test to be performed on site" from the Schedule of Activities During the Open-Label Treatment Phase.	This footnote refers to the urine drug test which occurs during a clinic visit and is not optionally remote.
1.1 Synopsis 4.1.1 Study Interventions 4.1.2 Screening Phase 6.9.1 Current (SSRI/SNRI) Antidepressant Therapy	Removed mentions of only one SSRI/SNRI being taken during the screening phase and specified that participants will be permitted to only continue 1 of the allowed antidepressants during the DB Treatment Phase.	It is not a requirement to be on one antidepressant during the screening phase, as medication can still be tapered off or stopped day before randomization day.
1.2 Schema	Updated second sentence of schema note to "Throughout the OL Treatment Phase, participants will receive adjunctive aticaprant along with their standard-of-care antidepressant therapy. It is recommended that participants continue the same SSRI/SNRI antidepressant therapy taken during the DB Treatment Phase. Changes to the current antidepressant therapy are	Updated to align with new language in Section 4.1.4.

Section number and Name	Description of Change	Brief Rationale
	allowed (per investigator's discretion) in the OL Treatment Phase."	
1.3 Schedule of Activities (SoA)	Removed "During the DB Treatment Phase" in footnote t and added text to clarify when the average QTcF will be used to assess clinically relevant abnormalities during the study phases.	Edited footnote t to clarify when QTcF is used to assess. Clinically relevant abnormalities for inclusion or post-treatment changes.
4.1.2 Screening Phase 6.9.1 Current (SSRI/SNRI) Antidepressant Therapy	Added language about how to address participants that are taking antidepressants other than allowed SSRI or SNRI and any medications listed on the MGH-ATRQ.	Added for clarification regarding participants with antidepressants other than allowed SSRI or SNRI and any medications listed on the MGH-ATRQ.
4.1.4 Open-Label Treatment Phase 6.6 Dose Modification 6.9.1 Current (SSRI/SNRI) Antidepressant Therapy	Removed "SSRI/SNRI".	Type of antidepressant therapy is not specified during Open-Label Treatment Phase as this can be changes to standard of care according to investigator discretion.
5.1 Inclusion Criteria	Removed criterion #20.	Criterion deleted based on feedback from sites and in order to improve recruitment.
5.2 Exclusion Criteria	Added "DSM-5" to exclusion criterion 23 and added a note identifying the DSM-5 sexual dysfunction definition.	Text added to specify where the diagnoses come from.
6.1 Study Intervention(s) Administered	Edited text about using a participant diary during Screening and Double-Blind Treatment Phases.	Text edited to be more concise.
	Added text permitting changes in the underlying treatment based on local practices during the Open-Label Treatment Phase.	Added text to clarify that changes can be made in the underlying treatment during the open label treatment phase.
6.9 Prior and ongoing therapy	Added language on capturing oral contraceptives and hormonal replacement therapy in the CRFs.	Hormonal treatment may influence the sexual function, therefore sites will be asked to document information about ongoing prestudy and concomitant oral contraceptives/hormonal replacement therapies.
	Removed language about when COVID-19 vaccine should be administered.	The window for COVID-19 vaccine administration is no longer needed.
6.9.1 Current (SSRI/SNRI) Antidepressant Therapy	Added language on providing a participant's diary for use in the Screening and Double-Blind Treatment Phases and specified only AxMP is used during the Double-Blind Treatment Phase.	Participant's diary is provided for both the Screening and Double-Blind treatment phases. Only AxMP is used during the Double-Blind Treatment Phase.
7.2.1 Withdrawal From the Use of Study Samples; 10.2.1 Regulatory and Ethical	Removed reference to optional research samples, informed consent to optional samples, and withdrawal of consent to optional samples.	No optional samples are being collected in the study as all research samples are mandatory.

Section number and Name	Description of Change	Brief Rationale
Considerations; 10.2.3 Informed Consent Process; 10.2.6 Storage, Use, Transfer, and Retention of Data and Samples for Additional Future Research		
	Added text describing the recommended order of assessments at baseline and review of inclusion and exclusion criteria.	Added text to clarify recommended order of assessments and review of inclusion and exclusion criteria.
	Removed two study-specific materials.	Removed study-specific materials that are not available.
	Added "if applicable" to the text describing that Participant Experience Interviews will be conducted by a third-party vendor.	Clarified that interviews will only be conducted by a third-party vendor if applicable.
	Removed "video" from text describing audio/video being captured on the vendor's conduit server.	Video is not being recorded.
8.2.1 Montgomery-Asberg Depression Rating Scale (MADRS)	Specified that the MADRS assessment may be audio recorded.	Specified that audio and not video is being recorded.
8.3.3 Electrocardiograms	Removed "during the DB and OL Treatment Phases" and added "medical stability for inclusion (during screening and baseline) and for QTc stopping criteria during the treatment phases" to the note listing phases where the average QTcF will be used to assess clinically relevant abnormalities.	Updated language to clarify when QTcF is used to assess. Clinically relevant abnormalities for inclusion or post-treatment changes.
9.3.2 Primary Endpoint/Estimand Analysis	Added language detailing approaches to be taken in case of convergence problems with the unstructured variance-covariance matrix before proceeding to implement a structured variance-variance matrix. Clarified that a sandwich variance estimator will be used if a structured covariance matrix is implemented.	Added to align with the feedback received from a major Health Authority.
10.1 Appendix 1: Clinical Laboratory Tests	Removed text describing FT_4 testing for participants with known hypothyroidism who have been controlled on stable treatment for at least 3 months prior to screening and changed language from "participants with known hypothyroidism" to "participants with a history of thyroid disease".	Removed for consistency to align with exclusion criterion #13, ie, FT_4 to be tested for all participants with an abnormal TSH value and those with a history of thyroid disease.
10.2.1 Regulatory and Ethical Considerations; 10.2.3 Informed Consent Process	Added notes for potential substudy for Participant Experience Interview data collection (Optional, only in select countries). Deleted the following sentence: After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating	Further clarifications are made in sections 10.2.1 and 10.2.3 regarding the potential sub study for Participant Experience Interview data collection (Optional, and only in select countries).

Section number and Name	Description of Change	Brief Rationale
	agreement to participate in the optional research component.	
10.2.12 Monitoring	Removed text describing that the first post initiation visit will be made as soon as possible after enrollment has begun.	Removed since the expected visit timing is described in the sponsor's internal monitoring guidelines.
10.4 Appendix 4: Contraceptive and Barrier Guidance	Edited the description of FSH level in the postmenopausal range.	New text more accurately describes the FSH level postmenopausal range.
10.6 Appendix 6: Prohibited Concomitant Therapies	Added language to clarify and align with section 6.9.2 that prohibited medications are prohibited during the Double-Blind Treatment Phase.	Clarified the time period for prohibited medications.
	Added note about how to proceed if a medication is part of the antidepressant treatment regimen.	Preference is to not have a gap between stopping anything in addition to the SSRI/SNRI and starting the add-on as it may unnecessarily worsen participant depression.
	Removed "7 days before" from "participant must be on monotherapy by 7 days before first dose of study intervention)".	Participants are not required to by on monotherapy by 7 days before first dose of study intervention.
	Edited text about opioids to describe that brief treatment with opiates can be discussed on a case-by-case basis.	Clarified details of how brief opiate treatment can be discussed.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted and corrected.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

ABV	alcohol-by-volume
ADHD	attention deficit hyperactivity disorder
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANH+	with moderate-to-severe anhedonia
API	active pharmaceutical ingredient
ASEX	Arizona Sexual Experiences Scale
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AxMP	Auxiliary Medicinal Product(s)
BMI	body mass index
CGI-S	Clinical Global Impression – Severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum observed drug concentration
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRO	Contract Research Organization
C-SSRS	Columbia Suicidality Severity Rating Scale
CSF	cerebrospinal fluid
CSFQ-14	Changes in Sexual Functioning Questionnaire – short form
CTM	Clinical Trial Manager
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
DB	double-blind
DR	delta receptor
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th Edition
ECG	electrocardiogram
eDC	electronic data capture
EEA	European Economic Area
eITT	enriched intent-to-treat
CCI [redacted]	[redacted]
[redacted]	[redacted]
EU	European Union
EW	early withdrawal
FAS	Full Analysis Set
FAS_SF	Full Analysis Set-Sexual Function
FDA	Food and Drug Administration
fITT	full intent-to-treat
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
FT_4	free thyroxine
FWER	family-wise error rate
CCI [redacted]	[redacted]
GCP	Good Clinical Practice
GI	gastrointestinal
HbA1c	hemoglobin A1c / glycated hemoglobin
hCG	human chorionic gonadotropin
HRT	hormonal replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee

IEC	Independent Ethics Committee
IM	intramuscular
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IWRS	interactive web response system
JEISR	Janssen Electronic Inbound Safety Reporting
KR	kappa receptor
KRA	kappa receptor antagonist
LS	least-squares
LTM	Local Trial Manager
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOI	monoamine oxidase inhibitors
MDD	major depressive disorder
MDE	major depressive episode
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MMRM	mixed model for repeated measures
MR	mu receptor
NAcc	nucleus accumbens
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
OL	open-label
PCC	protocol clarification communication
PCP	Phencyclidine
PD	pharmacodynamic(s)
CCI	[redacted]
PHQ-9	Patient Health Questionnaire, 9-item
PK	pharmacokinetic(s)
PQC	Product Quality Complaints
PRO	patient-reported outcome(s) (paper or electronic as appropriate for this study)
CCI	[redacted]
CCI	[redacted]
QTc	corrected QT interval
QTcF	corrected QT interval with Fridericia's formula
RO	receptor occupancy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID-CT	Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version
SD	standard deviation
SDF	sexual dysfunction
SF	sexual function
SHAPS	Snaith-Hamilton Pleasure Scale
SIGMA	Structured Interview Guide for the MADRS
SIQA	Site Independent Qualification Assessment
SoA	Schedule of Activities
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression study
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
$t_{1/2}$	half-life
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

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	Reports directly from the participant without interpretation by clinician or anyone else

1. PROTOCOL SUMMARY

1.1. Synopsis

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

IND: 111006
EU CTR NUMBER: 2024-511557-21

Aticaprant (JNJ-67953964) is a small molecule, high-affinity, selective kappa receptor antagonist (KRA). Aticaprant is orally bioavailable and suitable for once-daily administration. Aticaprant is being developed for adjunctive treatment of Major Depressive Disorder (MDD) in participants with prominent anhedonia.

KRAs have shown anxiolytic- and antidepressive-like effects in both animal models and humans with MDD. No medications are currently approved that *selectively* antagonize the KR. Selective blockade of the KR, without interacting with the mu receptors (MRs) or delta receptors (DRs), may result in improvement of residual symptoms of depression, namely anhedonia, lassitude, and amotivation.

The proposed Phase 3 study will evaluate the efficacy of aticaprant 10 mg once daily as adjunctive therapy to an antidepressant compared with adjunctive placebo in improving depressive symptoms in adult participants with MDD with moderate-to-severe anhedonia (MDD ANH+) who have had an inadequate response to current antidepressant therapy with a selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). Participants who have completed the double-blind (DB) Treatment Phase may be able to proceed to a 24-week open-label (OL) Treatment Phase of adjunctive aticaprant if the participant is willing and may benefit from continued adjunctive treatment according to clinical judgment.

BENEFIT-RISK ASSESSMENT: While the safety, tolerability, and efficacy of aticaprant have been studied in short-term studies (up to 8 weeks), the benefit-risk profile of adjunctive aticaprant therapy with longer treatment has not been established.

CCI [redacted] The Phase 2 studies 67953964MDD2001 and FAST-MAS demonstrated that a 10 mg once daily dose of aticaprant is generally safe, effective, and well tolerated in participants with MDD.

The scientific and clinical evidence supports aticaprant 10 mg once daily as a safe dose that would provide optimal efficacy in adjunctive treatment for depressive symptoms, where the ultimate goal is to also effectively treat the remaining residual symptoms including anhedonia. The DB Treatment Phase of this study will therefore assess a dosage of adjunctive aticaprant 10 mg once daily vs placebo on overall improvement of depressive symptoms in MDD ANH+ adult participants. The study will also assess the efficacy of adjunctive aticaprant treatment compared with placebo on improving self-reported anhedonia symptoms and on improving sexual function (SF), each being administered adjunctively with current antidepressant treatment. The information obtained to date regarding aticaprant suggests that the potential benefits to patients with MDD in fulfilling an unmet medical need outweigh the identified risks (eg, Adverse Drug Reactions). The OL Treatment Phase is designed to provide an opportunity for participants with MDD ANH+ who complete the DB Treatment Phase to receive OL adjunctive aticaprant (pending the investigator's clinical evaluation on whether participants would benefit from adjunctive treatment). A 24-week duration is provided to allow participants to receive an adequate long-term treatment course; this aligns with the recommended treatment duration for an antidepressant for those with MDD.

OBJECTIVES AND ENDPOINTS

Objectives: Double-Blind Treatment Phase	Endpoints: Double-Blind Treatment Phase
Primary	
• To evaluate the efficacy of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in adult participants with MDD with moderate-to-severe anhedonia (ANH+) who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI.	• Change from baseline (ie, Day 1 pre-randomization, and hereafter referred to as 'baseline') to Day 43 in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score.
Key Secondary To evaluate the efficacy of adjunctive aticaprant 10 mg compared with placebo in adult participants with MDD ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI on the following:	
• Anhedonia symptoms (patient-reported)	• Change from baseline to Day 43 in CCI [redacted] total score.
• Sexual function (patient-reported) in the subset of participants with sexual dysfunction (defined as CSFQ-14 total score ≤41 for female, or ≤47 for male) at baseline	• Change from baseline to Day 43 in Changes in Sexual Function Questionnaire – 14 items (CSFQ-14) total score.
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 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 CCI [redacted] 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.
Safety Safety will be assessed for all participants.	
• To assess the safety and tolerability of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant (SSRI/SNRI) in participants with MDD ANH+	• Adverse events (AE) including AEs of special interest (AESIs) • Vital signs including weight, body mass index (BMI) • Suicidality assessment using the C-SSRS • Laboratory values and ECGs

Objectives: Open-Label Treatment Phase	Endpoints: Open-Label Treatment Phase
Safety Safety will be assessed for all participants	
• To assess the long-term safety and tolerability of aticaprant 10 mg as adjunctive therapy to an antidepressant (SSRI/SNRI) in participants with MDD ANH+	• Adverse events (AE) including AEs of special interest (AESIs). • Vital signs including weight, body mass index (BMI). • Suicidality assessment using the C-SSRS. • Laboratory values and ECGs.
Efficacy To assess the long-term efficacy of aticaprant administered as adjunctive therapy to an antidepressant (SSRI/SNRI) in participants with MDD ANH+ on the following:	
• Depressive symptoms (clinician- and patient-reported)	• Change from OL baseline over time in the MADRS total score.

Objectives: Open-Label Treatment Phase	Endpoints: Open-Label Treatment Phase
	• Change from OL baseline over time in the PHQ-9 total score.
• Anhedonia symptoms (patient-reported)	• Change from OL baseline over time in the CCI total score.
• Sexual function (patient-reported) in the subset of participants with sexual dysfunction at baseline	• Change from OL baseline over time in CSFQ-14 total score.
• Severity of depressive illness (clinician-reported)	• Change from OL baseline over time in the CGI-S total score.
• Response rate (clinician-reported)	• Proportion of participants with ≥50% reduction from OL baseline in the MADRS total score over time.
• Remission of depressive symptoms (clinician-reported)	• Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤10, over time.

Hypothesis: The hypothesis for the DB Treatment Phase of 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. There is no formal hypothesis for the OL Treatment Phase of the study.

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

The study population will include adults, aged 18 to 64 years (inclusive) who meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for recurrent or single episode MDD, without psychotic features, based upon clinical assessment and confirmed by the Structured Clinical Interview for DSM-5 Axis I Disorders - Clinical Trials Version (SCID-CT). Participants must have symptoms of anhedonia based on clinical assessment and confirmed by presence of anhedonia (positive response to major depressive episode [MDE] module symptom Item 2) on the SCID-CT at screening and a Snaith-Hamilton Pleasure Scale (SHAPS) total score of CCI at screening and baseline visits. At the start of screening, all participants must have had an inadequate response to at least 1 and up to 5 (inclusive) oral antidepressant treatments, administered at an adequate dose (at or above the minimum therapeutic dose per Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [MGH ATRQ]) and duration (at least 6 weeks) in the current episode of depression. An inadequate response is defined as <50% reduction in depressive symptom severity as assessed by the MGH ATRQ, but with some improvement (>0%). This assessment of response must apply to the participant's current SSRI/SNRI antidepressant treatment. Additionally, participants must have moderate-to-severe depression with MADRS total score ≥25 during screening and baseline without a clinically significant improvement (ie, an improvement of more than 20% on their MADRS total score) between the screening and the baseline assessments. A Site Independent Qualification Assessment (SIQA) will assess the validity of the participants' current MDE, overall symptom severity, and antidepressant treatment response for inclusion in the study.

This study will consist of 4 phases: an eligibility screening phase (up to 30 days prior to first dose administration), a DB Treatment Phase (43 days), an OL Treatment Phase (24 weeks), and a Follow-up Phase (up to 14 days).

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

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

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

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

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

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

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

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

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

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

NUMBER OF PARTICIPANTS: Approximately 350 adult MDD ANH+ participants (18 to 64 years) will be enrolled in the study.

STUDY ARMS AND DURATION: A summary of the study arms, study intervention, dosage level, and route of administration are presented below.

Description of Interventions

Group/Arm Name	DB Treatment Phase (randomized to adjunctive aticaprant) and OL Treatment Phase	DB Treatment Phase (randomized to adjunctive placebo)
Intervention	Aticaprant/JNJ-67953964; 10 mg (1 orally administered tablet) once daily preferably in morning	Placebo; 1 orally administered tablet once daily preferably in morning

The maximum duration of participation in the study for an individual participant will be up to 36 weeks.

EFFICACY EVALUATIONS: The efficacy of the study intervention will be evaluated using clinician-rated scales: MADRS and CGI-S (depression); and patient-reported outcomes (PROs): SHAPS, CCI [redacted] PHQ-9, CCI [redacted] CSFQ-14, CCI [redacted]

PHARMACOKINETIC EVALUATIONS: Blood samples will be collected for the determination of plasma concentrations of aticaprant.

BIOMARKER EVALUATIONS: Blood samples will be collected to measure biomarkers related to [redacted]

SAFETY EVALUATIONS: Safety evaluations will include collection of AEs and concomitant medications, physical examinations, body weight, BMI, vital signs, 12-lead ECG, urine drug test, alcohol breath test, clinical laboratory tests, pregnancy tests, menstrual cycles tracking, and C-SSRS.

STATISTICAL METHODS

Sample Size Calculation: Approximately 350 participants will be enrolled in the study. Participants entering the DB Treatment Phase will be randomized in a 1:1 ratio to adjunctive aticaprant 10 mg or adjunctive placebo. [redacted]

Efficacy Analyses:

Primary Efficacy Endpoint: The primary efficacy endpoint is the change from baseline in MADRS total score at Day 43.

Primary analysis: Change from baseline in MADRS total score will be analyzed by MMRM based on observed case.

Key Secondary Endpoint: The following key secondary endpoints are defined in this study:

i. Change from baseline in [redacted] total score at Day 43

ii. Change from baseline in CSFQ-14 total score at Day 43

Key secondary analysis: Data will be analyzed using the same MMRM model as described for the primary 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 two-sided 0.05 level accounting for multiplicity due to the primary (MADRS total score) and the 2 key secondary efficacy endpoints ([redacted] total score, and CSFQ-14 total score). The testing procedure will first test the primary endpoint at two-sided 0.05 level. If the hypothesis corresponding to the primary endpoint is rejected, then the first key secondary endpoint ([redacted] total score) will be tested at 2- sided 0.05 level. If the hypothesis corresponding to the first key secondary endpoint is rejected, the testing will proceed to the second key secondary endpoint (ie, CSFQ-14 total score) at 2-sided 0.05 level. If the hypothesis corresponding to the primary endpoint or the first key secondary endpoint is not rejected, then the testing procedure will stop, and the endpoint(s) further down the testing sequence will not be tested.

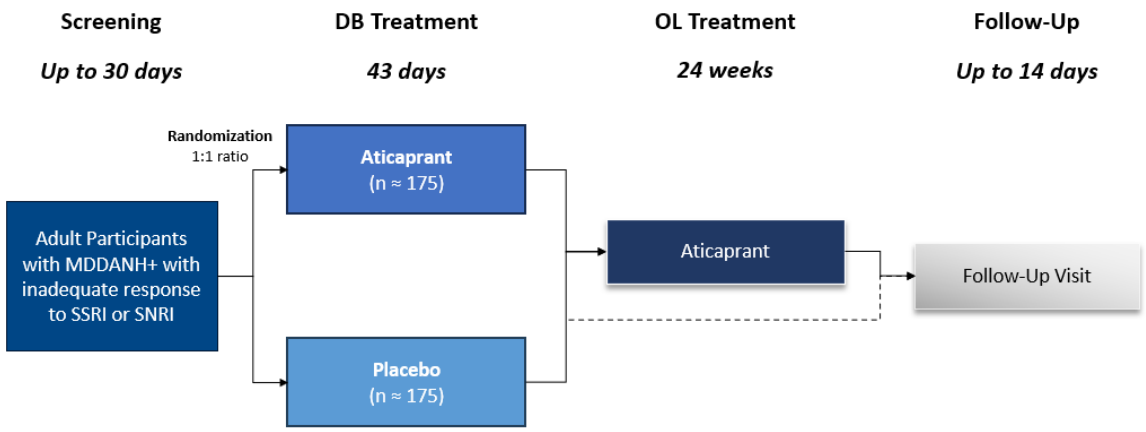
Efficacy Analyses in the OL Treatment Phase: The efficacy outcomes in the OL Treatment Phase will be summarized descriptively.

Safety Analyses: Safety data including but not limited to AEs, SAEs, AESIs [redacted], laboratory assessments, ECG measurements, and vital signs will be summarized by study intervention group. Suicide-related thoughts and behaviors based on C-SSRS will be tabulated by study intervention for each phase.

1.2. Schema

Figure 1: Schematic Overview of the Study

Abbreviations: ANH+ = with moderate to severe anhedonia; DB = double blind; MDD = major depressive disorder; OL = open label; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor



Notes:

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

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

1.3. Schedule of Activities (SoA)

Schedule of Activities During the Screening and Double-Blind Treatment Phase

Phase	Screening[a]		Double-blind Treatment					
Visit number	1.1	1.2[b,c]	2.1[r] DB Baseline	2.2	2.3	2.4	2.5	2.6[d] DB EOT/EW
Study Day	-30 to -2		1	8	15	22	29	43
Study Week	-4 to -1		1	2	3	4	5	7
Clinic Visit (**C**) or Remote Contact (**RC**)	**C**	**C or RC**	**C**	**RC**	**C**	**RC**	**C**	**C**
Visit window (days)				±2	±3	±2	±3	±3
Study Procedure								
Screening/Administrative								
Informed consent (ICF)[e]	X							
ICF for optional Participant Experience Interview[r]			X					
Medical History, psychiatric history, demographics	X							
Employment status	X							X
Inclusion/exclusion criteria[f]	X		X[p]					
SCID-CT	X							
MGH ATRQ	X							
SIQA[q]	X[p]							
Pre-study therapy	X							
Preplanned surgery/procedure(s)	X							
Diary for current antidepressant compliance (Dispense/Review)	X		X[p]		X		X	X
Evaluation of current antidepressant compliance[l]	X		X[p]				X	X
Serum pregnancy test[g]	X							
Urine pregnancy test[g]			X[p]				X	X
Menstrual cycle tracking (start date of last menstrual period prior to study visit)[h]	X		X					X
Height	X							
Weight	X		X[p]					X

Phase	**Screening**[a]		**Double-blind Treatment**					
Visit number	1.1	1.2[b,c]	2.1[r] DB Baseline	2.2	2.3	2.4	2.5	2.6[d] DB EOT/EW
Study Day	-30 to -2		1	8	15	22	29	43
Study Week	-4 to -1		1	2	3	4	5	7
Clinic Visit (**C**) or Remote Contact (**RC**)	**C**	**C or RC**	**C**	**RC**	**C**	**RC**	**C**	**C**
Visit window (days)				±2	±3	±2	±3	±3
Study Procedure								
Study Intervention Administration								
Randomization			X					
Dispense study intervention			X		X		X	
Oral Dose Study intervention[i]			Day 1 until and including Day 42					
Dispense/review study intervention diary[j]			X		X		X	X
Return/Drug Accountability					X		X	X
Efficacy Assessments[k]								
MADRS (Site Rater, SIGMA version)	X		X[p]		X		X	X
CGI-S (depression)			X[p]		X		X	X
SHAPS	X		X[p]					X
CCI			X[p]		X		X	X
CCI			X[p]		X		X	X
PHQ-9			X[p]		X		X	X
CCI			X[p]		X		X	X
CSFQ-14			X[p]		X		X	X
CCI			X[p]		X		X	X
CCI			X[p]		X		X	X
CCI			X[p]					X
CCI			X[p]				X	X
Safety Assessments								
Physical examination	X		X[p]					X
Vital signs	X		X[p]					X
12-lead ECG[s]	X		X[p]					X
Drug screen (urine)	X		X[p]				X	X

Phase	Screening[a]		Double-blind Treatment					
Visit number	1.1	1.2[b,c]	2.1[r] DB Baseline	2.2	2.3	2.4	2.5	2.6[d] DB EOT/EW
Study Day	-30 to -2		1	8	15	22	29	43
Study Week	-4 to -1		1	2	3	4	5	7
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	RC	C	RC	C	C
Visit window (days)				±2	±3	±2	±3	±3
Study Procedure								
Alcohol breath test	X		X[p]					
C-SSRS: Screening/Baseline version	X							
C-SSRS: Since last visit version			X[p]	X	X	X	X	X
Clinical Laboratory Tests								
Hematology, Chemistry	X		X[p]					X
Lipid panel (fasting)	X[u]							
Urinalysis	X		X[p]					X
TSH/FT_4; HbA1c	X							
Clinical Pharmacology Assessments								
Blood sample collection[m,n]								X
Biomarkers Assessments								
Morning blood sample collection[o]			X[p]					X
Ongoing Review								
Concomitant therapy	←		Continuous →					
Adverse events	←		Continuous →					

Abbreviations: C = Clinic Visit; CGI-S = Clinical Global Impression-Severity; CSFQ-14 = Changes in Sexual Functioning Questionnaire – short form; C-SSRS = Columbia Suicide Severity Rating Scale; CCI DB = Double-blind; ECG = electrocardiogram; EOT = End-of-Treatment; CCI EW = Early Withdrawal; FT_4 = free thyroxine; CCI HbA1c test = glycated hemoglobin test; MADRS = Montgomery-Åsberg Depression Rating Scale; MGH ATRQ = Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; CCI PHQ-9 = Patient Health Questionnaire, 9-item; CCI RC = Remote Contact; SCID-CT = Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version; SHAPS = Snaith-Hamilton Pleasure Scale; SIGMA = Structured Interview Guide for the MADRS; SIQA = Site Independent Qualification Assessment; TSH = thyroid-stimulating hormone.

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 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 SIQA and confirmation this was 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. Visit 1.2 can be skipped if the lipid panel was previously done.
d. If a participant prematurely discontinues from study intervention before the end of the DB Treatment Phase (ie, before completing Visit 2.6) for reasons other than withdrawal of consent, an EOT/EW visit (ie, Visit 2.6) should be conducted preferably the day after the last dose of study intervention, followed by the Follow-up Phase (ie, Visit 4.1). If Visit 2.6 is conducted on the same day as a scheduled visit, duplicate assessments are not required.
e. 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.
f. Verify inclusion/exclusion criteria before randomization of each participant.
g. Applicable to female participants of childbearing potential.
h. Only applicable to female participants with a menstrual cycle.
i. 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.
j. Dispense the study intervention diary at Visit 2.1 and review it at all clinical visits (C).
k. All PRO assessments should be completed first, prior to other assessments, and in the order listed in the above SoA table. Refer to Section 8 for more details about the order of assessments.
l. 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.
m. 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, and blood draw.
n. At Visit 2.6 (EOT/EW), a PK sample will be collected from all participants.
o. Biomarker samples will be collected under fasting conditions and prior to study intervention administration.
p. Study procedure or assessment must be performed before randomization.
q. SIQA remote interview will include an additional MADRS assessment performed by an independent rater during the screening phase to independently confirm site's evaluation of depression severity. The SIQA can be scheduled and completed within 7 to 14 days after Visit 1.1 and as soon as the site collects and enters all required information into eDC.
r. DB Visit 2.1 may be split in 2 consecutive days if needed. Assessments supporting inclusion or ruling out exclusion criteria must be performed early enough to obtain the results and confirm the eligibility prior to randomization. Please refer to the guidance on the recommended order of study procedures for information on how to organize the visit.

s. An optional Participant Experience Interview may be offered at selected study sites in select countries/territories. Consent may be offered once participant's eligibility is confirmed and should be obtained prior to the interview.
t. 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 medical stability for inclusion (during screening and baseline) and for QTc stopping criteria during the treatment phases.
u. Test can be performed at Visit 1.1 if the participant has come fasting.

Schedule of Activities During the Open-Label Treatment Phase

Phase	OL Treatment						Follow-up
	OL Baseline					OL EOT/EW	FU Visit
Visit Number	3.1[a]	3.2	3.3	3.4	3.5	3.6	3.7	4.1
Study Day	43							
Study Week	7	11	15	19	23	27	31	7-14 days after Visit 2.6 or 3.7 (EOT/EW)
Visit window (days)		±7	±7	±7	±7	±7	+7	
Clinic Visit (**C**) or Remote Contact (**RC**)	C	C	C	C	C	C	C	C
Study Procedure								
Screening/Administrative								
Urine pregnancy test[b]		X	X	X	X	X	X	
Menstrual cycle tracking[c]		X	X	X	X	X	X	
Weight				X			X	
Study Intervention Administration								
Dispense study intervention	X	X	X	X	X	X		
Dispense/review study intervention diary[h]	X	X	X	X	X	X	X	
Return/Drug accountability		X	X	X	X	X	X	
Study intervention administration[d]	← Continuous →							
Efficacy assessments[e]								
MADRS (Site Rater, SIGMA version)		X		X		X	X	X
CGI-S (depression)		X					X	X
CCI		X		X		X	X	X
PHQ-9				X			X	X
CSFQ-14		X		X		X	X	X

Phase	OL Treatment							Follow-up
	OL Baseline						OL EOT/EW	FU Visit
Visit Number	3.1[a]	3.2	3.3	3.4	3.5	3.6	3.7	4.1
Study Day	43							
Study Week	7	11	15	19	23	27	31	7-14 days after Visit 2.6 or 3.7 (EOT/EW)
Visit window (days)		±7	±7	±7	±7	±7	+7	
Clinic Visit (**C**) or Remote Contact (**RC**)	C	C	C	C	C	C	C	C
Safety assessments								
Physical examination							X	
12-lead ECG[f,g]							X	
Vital signs[f]		X					X	X
Urine drug test							X	
Alcohol breath test							X	
C-SSRS: Since last visit version		X	X	X	X	X	X	X
Clinical Laboratory tests								
Hematology, chemistry[f]			X		X		X	
Urinalysis			X		X		X	
Ongoing review								
Concomitant therapy	← Continuous →							
Adverse events	← Continuous →							

Abbreviations: C = Clinic Visit; CGI-S = Clinical Global Impression-Severity; CSFQ-14 = Changes in Sexual Functioning Questionnaire – short form; C-SSRS = Columbia Suicide Severity Rating Scale; CCI [redacted] DB = Double-blind; ECG = electrocardiogram; EOT = End-of-Treatment; EW = Early Withdrawal; FT_4 = free thyroxine; FU = Follow-up; CCI [redacted] MADRS = Montgomery-Åsberg Depression Rating Scale; PHQ-9 = Patient Health Questionnaire, 9-item; CCI [redacted] RC = Remote Contact.

Footnotes:

a. Results for all assessments performed at Visit 2.6 will not be repeated as part of Visit 3.1 and will serve as OL Baseline.
b. Applicable to female participants of childbearing potential.
c. Only applicable to female participants with a menstrual cycle.
d. 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.
e. All PRO assessments should be conducted in the order listed in the above SoA table. Refer to Section 8 for more details about the order of assessments.

f. 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.
g. 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 medical stability for QTc stopping criteria during the treatment phases.
h. Dispense the study intervention diary at Visit 3.1 and review it at all clinical visits (C).

2. INTRODUCTION

This study provides an opportunity to develop an improved treatment for mood disorders, based on a novel mechanism that is 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). KR activation by the endogenous opioid peptide, dynorphin, reduces both dopamine release in the NAcc and serotonin release from the dorsal raphe nucleus, and KR stimulation produces dysphoria, anhedonia, and depression-like behaviors in clinical studies and preclinical models of stress or addiction (Browne 2022; Bruchas 2010; Jacobson 2020; Knoll 2010; Lutz 2013; Schank 2012). Chronic stress, substance abuse, and acute withdrawal lead to increased dynorphin expression, activating KRs and subsequent downstream signaling pathways to inhibit mesolimbic dopamine surge, contributing to negative affective states in preclinical models (Carr 2010; Kivell 2014; Lalanne 2014; Shippenberg 2007; Van't Veer 2013). Moreover, KR *agonists* produce anxiogenic and depressogenic effects in experimental animals and humans, whereas KRAs have shown anxiolytic- and antidepressive-like effects in both animal models (Beardsley 2005; Knoll 2007; Land 2009; Mague 2003; Todtenkopf 2004) and humans with MDD. Furthermore, the therapeutic potential of KR antagonism has also been demonstrated in animal models of stress, anhedonia, depression, and anxiety as well as nicotine, heroin, and alcohol dependence (Beardsley 2005; Carr 2010; Jacobson 2020; Lutz 2014; Mague 2003; Marchette 2021; Rorick-Kehn 2014; Walker 2008). Based on this emerging body of scientific evidence, selective KR antagonism may provide therapeutic benefit in the treatment of MDD.

No medications are currently approved that *selectively* antagonize the KR. Selective blockade of the KR, without interacting with the MRs or DRs, may be useful from a clinical perspective to improve residual symptoms of depression which are mediated by the brain's reward circuitry, namely anhedonia, lassitude, and amotivation (Carlezon 2009; Krystal 2020).

Aticaprant (JNJ-67953964) is a small molecule, high-affinity, selective KRA. Aticaprant is orally bioavailable and suitable for once-daily administration. Aticaprant is being developed for adjunctive treatment of MDD in patients with prominent anhedonia.

Aticaprant has shown antidepressant-like effects in preclinical studies and had synergistic effects in mice 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). For example, Study 67953964MDD2001 provides proof of efficacy showing that after 6 weeks of treatment participants with MDD randomized to aticaprant 10 mg added to ongoing antidepressant achieved statistically significant and clinically meaningful reduction in overall depression severity on the MADRS (primary endpoint) compared with those who continued on the current antidepressant plus placebo.[redacted]

CCI [redacted]

For the most comprehensive nonclinical and clinical information regarding aticaprant, please refer to the latest version of the IB and IB Addenda.

The term "study intervention" throughout the protocol, refers to aticaprant or placebo 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

Major Depressive Disorder and Treatment Options

Depression is a common and serious psychiatric disorder affecting approximately 280 million individuals worldwide (according to the WHO 2023). Depression is a leading cause of disability worldwide and is associated with elevated mortality and suicide risk; patients with depression have a 10-year shorter life span due to increased mortality, including suicide (Walker 2015; WHO 2023).

Most of the current oral antidepressant pharmacotherapies target the same pathways (monoaminergic systems) (Artigas 2018; Strasburger 2017) and their effectiveness remains suboptimal for a significant portion of individuals diagnosed with depressive illnesses (Rush 2006b). In the seminal Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, only about one-third of patients with MDD were able to achieve remission after the first or second course of treatment (36.8% and 30.6%, respectively) using the currently approved drugs (Rush 2006b). Poor response to first-line treatments for MDD such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) remains a significant problem resulting in persistent impairment and high utilization of health care resources (Kennedy 2004). While current pharmacology can be effective in reducing depressed mood, other symptoms of depression such as anhedonia, insomnia, and fatigue have been reported to persist in patients even after treatment (Spijker 2001; Taylor 2010; Van Roekel 2017; Wardenaar 2012).

Anhedonia and Major Depressive Disorder

Anhedonia is defined as an impaired capacity to experience or anticipate pleasure (Berrios 1995; Ho 2013). It is one of the 2 core symptoms of depression and is defined in the DSM-5 as "markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day" (APA 2013). Anhedonia is a very common symptom of MDD, reported in approximately 75% of patients (Franken 2007), with the presence of either depressed mood and/or anhedonia required for a diagnosis of MDD (Moayedoddin 2013; Schrader 1997). As noted previously, in addition to

being a common symptom of MDD, anhedonia is a persisting residual symptom amongst individuals receiving treatment for MDD (Van Roekel 2017).

Increased severity of anhedonic symptoms is correlated with longer time to, as well as reduced likelihood of, disease remission, and increased frequency of relapse (Taylor 2010). Persistence of anhedonia has been linked to poorer outcomes in patients with MDD. The presence of anhedonia has been found to predict: the risk of a depressive episode within 2 years (Wardenaar 2012); increased severity of depressive symptoms (Gong 2017); a chronic course of depression over a 10-year period (Moos 1999); and longer time to remission (McMakin 2012; Spijker 2001) even when adjusting for overall depression severity (Uher 2012). Patients with MDD and anhedonia have greater social impairment and higher scores on measures of depression and hopelessness when compared with those with MDD without anhedonia (Fawcett 1983). The association of anhedonia with functional impairment was shown in a study of outpatients with MDD, where improvement in anhedonia over the 10- to 14-week study strongly predicted improvements in psychosocial functioning (Vinckier 2017). Patients with MDD who have higher levels of anhedonia also reported reduced quality of life compared with patients with MDD who had lower levels of anhedonia (Nakonezny 2010).

Despite anhedonia being a common, persistent, and disabling symptom in patients with MDD, there is currently no approved treatment available targeting this MDD dimension. The relatively few existing AD agents evaluated with respect to their effect on MDD and anhedonia have not shown pronounced collinear improvements in anhedonia symptoms (Cao 2019b). As such there is an unmet need to identify new more targeted treatments addressing depression symptoms that are insufficiently managed by current ADs (Uher 2012).

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 (MR), delta (DR) and kappa (KR). The mu receptor system is involved in analgesia, respiratory control, gastrointestinal motility and is also believed to be involved in addiction. Delta receptors are also widely found throughout the brain and are involved in mediation of stress, anxiety, and neuroprotection. KRs are found on postsynaptic mesolimbic neurons and are involved in modulation of dopamine release in the nucleus accumbens. The distribution of KRs in human brain has been described by in vivo PET imaging with the selective KRA [11C]-LY2795050 and dose-dependent occupancy has been demonstrated by aticaprant (Naganawa 2014; Naganawa 2016).

While several antagonists and agonists of the MR have been approved for use in humans, no medications are currently approved which selectively antagonize the KR. Aticaprant is a potent high-affinity KRA, showing a dose-dependent increase in KR occupancy with demonstrated selectivity over MR and DR. Selective blockade of the KR, without interacting with the MRs or DRs, is thought to be useful from a clinical perspective to dampen the effect of overactivation in the brain's reward circuitry. Selective modulation of the KR may modulate the brain's reward circuitry, resulting in improvement of residual symptoms of anhedonia, lassitude, and amotivation (Carlezon 2009; Krystal 2020). The therapeutic potential of KR antagonism has been demonstrated in animal models of anhedonia, depression, and anxiety, with KRAs reducing the signs of nicotine,

heroin, and alcohol withdrawal in rodent models of dependence (Beardsley 2005; Carr 2010; Lutz 2014; Mague 2003; Rorick-Kehn 2014; Walker 2008).

Functional effects of KR blockade by aticaprant on reward circuitry in human brain has been evaluated in a Phase 2 a study ("FAST-MAS"). The results of this study established that KR 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. This proof-of-concept trial demonstrated that engaging KRs can modulate neuronal circuits relevant to reward and hedonic response (Krystal 2020; Pizzagalli 2020). In the same study, significant reduction in severity of symptoms of anhedonia was seen on the SHAPS ($p=0.0345$) in patients with mood-anxiety spectrum and anhedonia symptoms, and significant treatment effects were seen on the temporal experience of pleasure scale (TEPS) consummatory subscale ($p<0.02$), although not on the anticipatory subscale (Krystal 2020; Pizzagalli 2020).

In the Phase 2 Study 67953964MDD2001, MDD participants randomized to aticaprant 10 mg added to ongoing antidepressant therapy achieved statistically significant greater reduction in overall depression severity on the MADRS after 6 weeks of treatment compared to those who continued just on their current antidepressant plus placebo. CCI [redacted]

Sexual Dysfunction

Sexual dysfunction (SDF), defined as a disturbance in desire (ie, libido), arousal (eg, penile erection or vaginal lubrication), and orgasm, is common in untreated patients with MDD and additionally occurs as an adverse reaction to the serotonergic antidepressants commonly used to treat MDD (Kennedy 2009). Consequently, SDF is widely associated with depression and is twice as common in patients with depression compared to healthy controls (Angst 1998). Estimates of the percentage of patients on SSRIs who experience treatment-related SDF vary widely but range from 25% to 90% depending on the method of assessment and number of sexual symptoms assessed (Delgado 2005; Higgins 2010; Labbate 2001; Montejo 2001, Pecina 2019; Rosen 1999; Serretti 2009). Although successful treatment of depression may alleviate SDF in some patients, the available evidence suggests that most patients treated with SSRI/SNRIs continue to experience SDF for prolonged periods irrespective of improvement in depressive symptoms. Strategies for alleviating SSRI/SNRI-associated SDF in patients being treated for MDD include reduction in medication dose, add-on therapy with agents that enhance dopamine levels or that affect specific serotonin receptors, switch to an antidepressant associated with less SDF, or use of nonpharmacological approaches (such as psychotherapy, exercise or yoga). However, none of these strategies have been fully or robustly successful to date (Montejo 2019) and for patients with MDD, SDF remains a major driver of treatment noncompliance to their antidepressant therapy; which can further exacerbate depressive symptoms and negatively impact health-related quality of life (Rosen 1999).

The sexual side effects of SSRIs/SNRIs putatively result from inhibition of the serotonin (5-HT) transporter and increased serotonergic activation of the 5-HT2 and 5-HT3 receptors (Labbate 2003). CCI [redacted]

CCI [redacted]

The proposed study is a randomized, DB, multicenter, placebo-controlled study to evaluate the efficacy of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms in adult participants with MDD ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI or SNRI. Participants who complete the DB Treatment Phase of the trial have the option of continuing treatment in the OL Treatment Phase.

2.2. Background

Aticaprant (JNJ-67953964, previously known as CERC-501 and LY2456302) is a small molecule, high-affinity KRA. Aticaprant is orally bioavailable and suitable for once-daily administration.

KRs and their endogenous ligand dynorphin are localized in areas of the brain that affect reward and stress, and may play a key role in mood, stress, and addictive disorders (Bruchas 2010; Knoll 2010; Schank 2012). Chronic stress, substance abuse, and acute substance withdrawal lead to increased dynorphin release, activating KRs, and subsequent downstream signaling pathways to inhibit mesolimbic dopamine surge, contributing to negative affective states. The behavioral pharmacology of KR antagonism has been tested in animal models of anhedonia, depression, and anxiety, and found to have meaningful effects that may translate to therapeutic benefit in humans.

It is hypothesized that by modulating the negative affective state associated with stress response, KRAs may be effective for the treatment of patients with mood disorders.

Nonclinical Studies

Nonclinical Pharmacology

Aticaprant (JNJ-67953964) is a potent, high-affinity antagonist (inhibition constant [Ki]=0.807 nM) for KRs, with demonstrated selectivity over MRs and DRs, as assessed by in vitro binding and functional assays. CCI [redacted] 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.

CCI [redacted]

CCI [redacted]

[redacted]

Safety Pharmacology

CCI [redacted]

CCI [redacted]

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).

CCI [redacted]

CCI [redacted]

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

Aticaprant is orally bioavailable and brain penetrant. Aticaprant is highly protein bound (>99%) in human, dog, rat, and mouse plasma. Metabolism is primarily through CCI [redacted]

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 postdose, 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 (percent 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 $t_{1/2}$ 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 (Study I2Z-MC-LAFB [Lowe 2014]; dose: 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.

CCI

Efficacy Studies

A completed Phase 2a investigator-initiated study (FAST-MAS) designed to determine whether KR 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=43) 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 TEPS consummatory subscale ($p<0.02$). CCI

CCI [redacted] (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. CCI [redacted]

The Phase 2 study 67953964MDD2001 showed greater reduction in overall depression severity on the MADRS in participants with MDD treated with aticaprant 10 mg added to their 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. CCI [redacted]

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 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 TEAE 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 adjunctive aticaprant 10 mg experienced a TEAE, compared with 35.7% of participants receiving adjunctive placebo. The most common TEAEs during the treatment phase were (aticaprant vs placebo) headache (11.8% vs 7.1%) and diarrhea (8.2% vs 2.4%). TEAEs of special interest in the aticaprant group that were commonly reported were[redacted] (5.9% each in the aticaprant group vs 0.0% in placebo).

Similarly, in the FAST-MAS Study, aticaprant given as a monotherapy 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%).

[redacted]

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. Risks for Study Participation

AEs of CCI [redacted] are considered to be of special interest in this study. Information about these events and instructions for investigators on assessing, monitoring, and reporting these are provided in the IB, Section 8.4.7, and Section 10.3.3.

Participants will be carefully monitored during the study and participants who are unable to tolerate the study intervention will be withdrawn from the study. If necessary, the investigator may immediately stop study intervention.

Assessment of the potential efficacy of a new compound for the treatment of major depression requires adequate and well-controlled clinical studies. This study will evaluate the efficacy of aticaprant 10 mg compared with placebo as adjunctive therapy to an antidepressant in improving depressive symptoms. In a meta-analysis of drug studies conducted in MDD, it was reported that adult participants did not have higher rates of suicide behaviors or attempts in the placebo group compared with those receiving an active antidepressant (Kahn 2000). These studies showed annual suicide rates of 0.8% on the investigational drug, 0.7% on the active comparator, and 0.4% on placebo. Thus, the risk of irreversible harm was not higher in the placebo arm compared with the active control arms. Therefore, the use of an active-controlled study allows for assessment of efficacy of a new compound to allow for scientifically meaningful results.

Safety evaluations will include evaluation of suicidal ideation/behavior at each contact. At any point in the study, the participant may withdraw consent or be removed from the study by the investigator if they cannot tolerate study intervention or if there are any other clinical concerns.

2.3.2. Benefits for Study Participation

There is evidence to suggest that, with the targeted mechanism of action, selective KR antagonism may result in improvement of symptoms of depression linked to impaired functioning in the reward circuitry (like anhedonia and amotivation) (Borsini 2020), which are presently 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 KRAs in the treatment of MDD ANH+.

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 an ongoing antidepressant with inadequate response, compared with those who continued on their current antidepressant plus placebo. CCI [redacted] (see Section 2.2). Furthermore, aticaprant was generally safe and well tolerated. Participants in this study will help evaluate the use of aticaprant in the treatment of MDD, specifically MDD ANH+, and increase understanding of the disease indication.

CCI [redacted] Given the prevalence and burden of SDF in patients with MDD receiving SSRI/SNRIs, adjunctive aticaprant treatment may provide additional treatment benefit for these MDD patients. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering from MDD and offers potential public health benefits.

Finally, 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.

2.3.3. Benefit-risk Assessment for Study Participation

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 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, changes in vital sign measurements, 12-lead ECGs, or clinical laboratory evaluations reported (see Section 2.2).

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

CCI [redacted]

The information obtained to date regarding aticaprant suggests that the potential benefits to patients with MDD in fulfilling an unmet medical need outweigh the identified risks (eg, ADRs).

3. OBJECTIVES AND ENDPOINTS

Double-Blind Treatment Phase

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

CCI [redacted]

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

Open-Label Treatment Phase

Objectives	Endpoints
Safety Safety will be assessed for all participants	
• To assess the long-term safety and tolerability of aticaprant 10 mg as adjunctive therapy to an antidepressant (SSRI/SNRI) in participants with MDD ANH+	• Adverse events (AE) including AEs of special interest (AESIs). • Vital signs including weight, body mass index (BMI). • Suicidality assessment using the C-SSRS. • Laboratory values and ECGs.
Efficacy To assess the long-term efficacy of aticaprant administered as adjunctive therapy to an antidepressant (SSRI/SNRI) in participants with MDD ANH+ on the following:	
• Depressive symptoms (clinician- and patient-reported)	• Change from OL baseline over time in the MADRS total score. • Change from OL baseline over time in the PHQ-9 total score.
• Anhedonia symptoms (patient-reported)	• Change from OL baseline over time in the CCI total score.
• Sexual function (patient-reported) in the subset of participants with sexual dysfunction at baseline	• Change from OL baseline over time in CSFQ-14 total score.
• Severity of depressive illness (clinician-reported)	• Change from OL baseline over time in the CGI-S total score.
• Response rate (clinician-reported)	• Proportion of participants with ≥50% reduction from OL baseline in the MADRS total score over time.
• Remission of depressive symptoms (clinician-reported)	• Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤10, over time.

Additional exploratory objectives during both the Double-Blind and Open-Label Treatment Phases



ESTIMANDS

The primary efficacy estimand is provided in Section 9.3.2 and the key secondary estimands are provided in Section 9.3.3.

Refer to Section 8 for evaluations related to endpoints.

HYPOTHESIS

The hypothesis for the DB Treatment Phase of this study is that adjunctive treatment with aticaprant 10 mg is superior to adjunctive 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.

There is no formal hypothesis for the OL Treatment Phase. The OL Treatment Phase is designed to provide an opportunity for participants with MDD ANH+ who complete the DB Treatment Phase to receive OL adjunctive aticaprant (pending the investigator's clinical evaluation on whether participants would benefit from adjunctive treatment). A 24-week duration is provided to allow all participants to receive an adequate long-term treatment course; this aligns with the recommended treatment duration for an antidepressant (Bauer 2013; Rush 2006a).

4. STUDY DESIGN

4.1. Overall Design

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

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

This study will consist of 4 phases:

- an eligibility screening phase (up to 30 days prior to first dose administration),
- a Double-blind Treatment Phase of 43 days,
- an Open-label Treatment Phase of 24 weeks,
- and a Follow-up Phase of up to 14 days.

Approximately 350 adult MDDANH+ participants (18 to 64 years) will be enrolled in the study. Participants entering the DB Treatment Phase will be randomized in a 1:1 ratio to adjunctive aticaprant 10 mg or adjunctive placebo.

An Independent Data Monitoring Committee (IDMC) will be commissioned for this study to periodically review safety data. Refer to Committees Structure in Section 10.2.7 for details.

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

4.1.1. Study Interventions

Participants will be randomized in the DB Treatment Phase to receive adjunctive aticaprant 10 mg or adjunctive placebo. The study intervention will be administered orally as 1 film-coated tablet once daily, around the same time and preferably in the morning.

In the screening and the DB Treatment Phase, all participants will continue their current SSRI/SNRI antidepressant therapy at the same dose without change as prior to entering the study and taken around the same time of the day as prior to entering the Screening and DB Treatment Phase.

All participants enrolled in the OL Treatment Phase will receive OL aticaprant treatment at a dose of 10 mg once daily without breaking the blind from the DB Treatment Phase. During the OL Treatment Phase, participants will continue taking standard-of-care antidepressant therapy to which aticaprant will be added.

The maximum duration of participation in the study for an individual participant (including Screening, DB Treatment and Follow-up Phases) will be up to 36 weeks (up to 30 days for Screening, 43 days for the DB Treatment Phase, 24 weeks for the OL Treatment Phase, and up to 14 days for the Follow-up Phase).

4.1.2. Screening Phase

After providing signed informed consent, all participants experiencing a major depressive episode (MDE) will be screened to evaluate their eligibility for study participation.

Evaluations that will be performed at each visit during this phase are outlined in the SoA (Section 1.3).

At screening, participants must:

- Meet DSM-5 diagnostic criteria for recurrent or single episode MDD, without psychotic features, based upon clinical assessment and confirmed by the SCID-CT

  and

- Have symptoms of anhedonia based on:
  - Clinical assessment and confirmed by presence of anhedonia (positive response MDE module symptom Item 2) on the SCID-CT

    and

  - Self-reported assessment (SHAPS total score[redacted] at screening and at DB baseline).

At the start of screening participants must have had an inadequate response to at least 1 and up to 5 (inclusive) oral antidepressant treatments, administered at an adequate dose (at or above the minimum therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current depressive episode (see Section 5.1, Inclusion Criterion 7). 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 as assessed by MGH ATRQ, 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). This assessment of response must apply to the participant's current SSRI/SNRI antidepressant treatment.

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

A SIQA as performed by a remote rater will assess the validity of the participants' current MDE, overall symptom severity, and antidepressant treatment response for inclusion in the study.

All participants will continue their current SSRI/SNRI antidepressant therapy for the duration of the Screening Phase and DB Treatment Phase. The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. During the DB Treatment Phase of the study, participants will be permitted to only continue 1 of these allowed antidepressants at an adequate and tolerated dose during the study. Other antidepressants and any medications listed on the MGH-ATRQ taken in addition to the current SSRI or SNRI, including for reasons other than depression (eg, insomnia or anxiety) will be tapered (if applicable) after completion of the SIQA and confirmation that this was passed, and discontinued prior to the first dose of study intervention. No changes in the current SSRI/SNRI antidepressant or dose are permitted from screening until the end of the DB Treatment Phase (see Section 6.9.1 for details). The sponsor will not supply these antidepressant medications.

Prohibited medications will be prohibited from 1 week prior to the first dose of study intervention in the DB Treatment Phase until after the last dose of study intervention in the DB Treatment Phase. Tapering or time of discontinuation of a prohibited medication during the screening phase should be based on potential drug-drug interactions, local prescribing information, or clinical judgment (see Section 6.9.2 and Section 10.6 for details).

Tapering and discontinuation of any ongoing prohibited therapies should be initiated after completion of the SIQA and confirmation that this was passed. If needed (eg, a longer tapering required for prohibited therapies or other circumstances) the screening phase may be extended for up to 3 additional weeks after consultation with sponsor's Medical Monitor or designee. Eligible participants who do not require a tapered discontinuation of their prohibited treatment(s) can immediately proceed into the DB Treatment Phase and can have their DB baseline visit (ie, Visit 2.1) on the next day following Visit 1.2, provided eligibility is confirmed.

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 throughout the study. No dose increases of the benzodiazepines beyond the equivalent of 4 mg/day of lorazepam or start of new benzodiazepine medications are permitted during screening and the DB Treatment 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. AEs will be collected from the time a signed and dated 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 scheduled End-of-Treatment (EOT) on Day 43 or premature discontinuation of study intervention (ie, Early Withdrawal [EW]). 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 therapy (one only) at the same dose without change and taken 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 responsible site staff personnel. The DB aticaprant treatment and use of the current SSRI/SNRI treatment will be captured in the participant paper diaries.

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

Participants who have completed the DB Treatment Phase as defined above may be eligible to continue in the OL Treatment Phase. 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 OL Treatment Phase. The decision to enroll in the OL Treatment Phase or enter the Follow-up Phase will be documented in the electronic case report form (eCRF).

Eligible participants who decide to participate in the OL Treatment Phase will proceed to the OL Treatment Phase immediately and will not complete the Follow-up Phase until after the OL Treatment Phase (see Section 4.1.4). Participants who discontinue study intervention early (ie, prior to completion of Day 43 Visit) or who are noncompliant 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 continue in the OL Treatment Phase. Missing study intervention doses due to temporary interruption (eg, adverse event per Section 7.1.3 or other clinically relevant reason, etc) 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 continuing to the OL Treatment Phase, will complete the EW/EOT Visit (Visit 2.6, see Section 1.3) and will then enter the Follow-up Phase of the study (Visit 4.1, see Section 1.3).

End-of-Treatment/Early Withdrawal Visit

The EOT/EW Visit (Visit 2.6) 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.

4.1.4. Open-Label Treatment Phase

For participants who continue in the OL Treatment Phase, assessments performed on Day 43 of the DB Treatment Phase (Visit 2.6) will not be repeated at the start of the OL Treatment Phase (Visit 3.1). Results for all assessments performed at Visit 2.6 will serve as OL Baseline.

During the OL Treatment Phase, all eligible participants will receive OL aticaprant treatment of 10 mg once daily starting on Day 43 (OL Baseline, Visit 3.1).

All eligible participants should take their assigned study intervention at home, once daily, from Day 43 through Week 31 (EOT, Visit 3.7), preferably in the morning.

Throughout the OL Treatment Phase, participants will receive adjunctive aticaprant along with their standard-of-care antidepressant therapy. It is recommended that participants continue the same SSRI/SNRI antidepressant therapy taken during the DB Treatment Phase. Changes to the current antidepressant therapy are allowed (per investigator's discretion) in the OL Treatment Phase with the reason documented in the source documents and participant's eCRF.

Participants who discontinue study intervention during the OL Treatment Phase will complete the EW/EOT Visit (Visit 3.7, see Section 1.3) and will then enter the Follow-up Phase of the study (Visit 4.1, see Section 1.3 and Section 4.1.5).

Safety and efficacy assessments, biomarker sampling, and other study procedures will be performed per the SoA.

End-of-Treatment/Early Withdrawal Visit

The EOT/EW Visit (Visit 3.7) will take place at Week 31 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.

4.1.5. Follow-up Phase

At the start of the Follow-up Phase, further clinical/standard-of-care treatment for depression will be arranged by the study investigator and/or the participant's treating physician. Changes to the current antidepressant treatment are permitted in this study phase. Study intervention will not be administered during this phase.

Evaluations that will be performed at each visit during this phase are outlined in the SoA (Section 1.3).

Follow-up Visit

Participants should return to the study site for a follow-up visit (ie, Visit 4.1) within 7 to 14 days after Visit 2.6 (DB EOT/EW) (Section 4.1.3) or 3.7 (OL EOT/EW) (Section 4.1.4). At the follow-up visit, safety and efficacy assessments/procedures will be completed per the SoA (Section 1.3).

4.2. Scientific Rationale for Study Design

Up to 70% of individuals who are on AD therapy are inadequately treated for their depression (Rush 2006b). 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. CCI [redacted]

The clinical outcomes in Study 67953964MDD2001 are complemented by the results from an investigator-initiated study FAST-MAS (Krystal 2020), which showed that KR 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 KR, aticaprant can modulate neuronal circuits relevant to reward and hedonic response.

CCI [redacted]

4.2.1. Study Population

The study population will include participants from the general MDD population (adults aged 18 to 64 years, inclusive) with an inadequate response to their current ongoing standard-of-care antidepressant (SSRI/SNRI) who are moderate to severely depressed with ANH+. The primary and key secondary analyses will be assessed from baseline to Day 43.

The proposed design for enrollment of participants 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 participants with moderate-to-severe anhedonia (MDD ANH+).

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

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

DB Treatment Phase

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

OL Treatment Phase

Participants who proceed to the OL Treatment Phase of this study will start with aticaprant 10 mg once daily (regardless of their treatment assignment in the DB Treatment Phase which will remain blinded).

4.2.3. Duration of Treatment Phases

The 6-week duration of the DB Treatment Phase was chosen to provide sufficient time for the onset of efficacy of aticaprant added to the current antidepressant and is consistent with the duration of the ongoing short-term Phase 3 studies (67953964MDD3001 and 67953964MDD3002) with aticaprant. Based on an FDA conducted meta-analysis of data from 24 short-term antidepressant studies submitted to this Agency over a 10-year period, the antidepressant-placebo treatment difference was consistent for studies with a duration of 4 to 8 weeks, suggesting that a duration of 6 weeks is adequate to obtain evidence of initial response (Khin 2013; Yang 2013). Furthermore, the 6-week duration of the DB Treatment Phase is consistent with the duration suggested in the CHMP guideline for clinical studies in depression (EMA Guideline on Clinical Investigation of Medicinal Products in the Treatment of Depression 2013).

For the OL Treatment Phase, a 24-week duration is provided to allow participants to receive an adequate long-term treatment course; this aligns with the recommended treatment duration for an antidepressant treatment course for major depression (Bauer 2013; Rush 2006a).

4.2.4. 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 duration of the DB Treatment Phase is short, minimizing the time on adjunctive placebo. All participants will continue their current SSRI/SNRI antidepressant therapy (one only) at the same dose without change throughout the DB Treatment Phase and the study intervention/placebo will be added to it. 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 while experiencing moderate-to-severe depression and anhedonia will be enrolled (pending the investigator's clinical evaluation on whether participants would benefit from adjunctive treatment). 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. Participants will be monitored very closely with in-person visits and remote contacts throughout the study. 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 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.

Aticaprant will be made available through the OL Treatment Phase for all eligible participants who complete the 6-week DB Treatment Phase.

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time frame. The approximate blood volume to be collected is 76 mL, which is less than a Red Cross blood donation.

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

4.2.5. CCI

CCI

[redacted]

4.2.6. Participant Input Into Design

A Global Patient Council of patients with MDD was consulted. Participants provided insights on the study intervention, the trial design, eligibility criteria, the patient journey, and required assessments. They also shared where they perceived as barriers to participation and potential benefits of participation.

Based on this participant input, information was collected and evaluated and, if relevant, implemented in protocol or in operational aspects.

The results of the study may be made available to all participants through a plain language summary; a technical summary of results on clinicaltrials.gov and/or clinicaltrialsregister.eu and/or other national registries at the conclusion of the study according to local standards/restrictions.

4.3. Justification for Dose

The aticaprant 10 mg once daily 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.

CCI [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 CCI [redacted] cleared and is primarily metabolized through CCI [redacted] and CCI [redacted] which may provide rationale not to expect any age effect on the PK in adults up to 64 years, inclusive, included in this study.

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 Schedule of Activities (Section 1.3) 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.

Participant Study Completion Definition

A participant will be considered to have completed the DB Treatment Phase if he or she has completed the Day 43 Visit of the DB Treatment Phase (Visit 2.6), including the MADRS assessment at the end of the 6-week DB Treatment Phase (ie, Day 43 MADRS), and has not discontinued study intervention during the DB Treatment Phase.

A participant not entering the OL Treatment Phase will be considered to have completed the study if he or she completed the above-mentioned DB visits and assessments, and the Follow-up Phase (Visit 4.1), including MADRS and CCI [redacted] assessments at this visit.

A participant will be considered to have completed the OL Treatment Phase if he or she has completed the Week 31 Visit of the OL Treatment Phase (Visit 3.7), including the MADRS assessment at the end of the 24-week OL Treatment Phase, and has not discontinued study intervention during the OL Treatment Phase.

A participant entering the OL Treatment Phase will be considered to have completed the study if he or she completed Visits 2.6 and 3.7 in the DB Treatment Phase and OL Treatment Phase, respectively, and the Follow-up Phase (Visit 4.1), including MADRS and CCI [redacted] 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, Screen Failures for conditions under which rescreening may be allowed.

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.

5.1. Inclusion Criteria

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

Age

1. Adults aged 18 (or the legal age of consent in the jurisdiction in which the study is taking place) to 64 years, inclusive.

Type of Participant and Disease Characteristic(s)

2. Be medically stable based on physical examination (including a brief neurologic examination), medical history, vital signs (including blood pressure), and 12-lead ECG performed at screening and DB 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 participant's source documents and initialed by the investigator.

3. Be medically stable based on clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, retesting 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 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.

5. Have symptoms of anhedonia based on clinical assessment and confirmed by presence of anhedonia (positive response to MDE module symptom Item 2) on the SCID-CT at screening.

6. Have a SHAPS total score of CCI at screening (Visit 1.1) and DB baseline (Visit 2.1) visits.

7. Have had an inadequate response to at least 1 and up to 5 (inclusive) oral antidepressant treatments (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 as assessed by the MGH ATRQ, 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). This assessment of response must apply to the participant's current SSRI/SNRI antidepressant treatment.

8. Is currently receiving and tolerating well any one of the following SSRI or SNRI antidepressants at screening, in any approved formulation and available in the participating country/territory: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, or 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 who have normal renal and hepatic function may enter the study.

9. Have moderate-to-severe depression with MADRS total score ≥25 during screening (Visit 1.1 [assessed by the site rater and by the independent rater during the SIQA]) and DB Baseline (Visit 2.1 [assessed by site rater]) and must not demonstrate a clinically significant improvement (ie, an improvement of more than 25% on their MADRS total score) between the screening (Visit 1.1) and DB Baseline (Visit 2.1) site-rater assessments.

10. Participant's MDE, symptom severity and treatment response must be deemed "valid" using the SIQA (**Note**: the SIQA interview will include an additional MADRS assessment performed by an independent remote rater during the screening phase to independently confirm site's evaluation of depression severity).

11. Must be an outpatient at screening.

Weight

12. BMI between 18 and 40 kg/m^2 (inclusive).

Sex and Contraceptive/Barrier Requirements

13. A female participant of childbearing potential must have a negative highly sensitive serum (hCG) pregnancy test at screening and a negative urine pregnancy test pre-dose at DB baseline.

14. A female participant must be (as defined in Section 10.4):

    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 1 month 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.

15. 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.

16. A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study intervention.

    Male participants must also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak; see Section 10.4.

    Note: Use of condom as the sole method of contraception is not considered to be a highly effective method of contraception; see Section 10.4.

17. 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.

18. Have had satisfactory sexual functioning before the onset of the current depressive episode or start of the current antidepressant treatment (based on participant's report during screening diagnostic interview).

Informed Consent

19. 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.

Other Inclusions

20. Criterion deleted per Amendment 1.

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. Has had no response (treatment failure) to 2 or more consecutive antidepressant treatments administered at an adequate dose (at or above the minimum therapeutic dose) and duration (at least 6 weeks) in the current episode of depression including the current SSRI/SNRI (ie, the one to be continued in the treatment phases) assessed using the MGH ATRQ.

2. Has one or more of the following diagnoses:

    - A current or prior (lifetime) DSM-5 diagnosis of:
        - a psychotic disorder or MDD with psychotic features (confirmed by the SCID-CT)
        - 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
    - A primary DSM-5 diagnosis (which has been the primary focus of psychiatric treatment within the past 2 years) of:
        - 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.

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. Has in the current depressive episode had vagal nerve stimulation or deep brain stimulation device in the current episode or has had an inadequate response to an adequate course of intravenous or intranasal ketamine or esketamine (>2 treatments), or electroconvulsive therapy (ie, at least 7 treatments).

6. Has 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 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) for suicidal ideation on the C-SSRS, 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 DB 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).

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

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

10. Has a history of, or symptoms and signs suggestive of liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR ALT or AST values ≥3 x ULN OR total bilirubin >1.5 x the ULN in the screening phase.

    - Repeat of screening test for abnormal ALT and AST is permitted during the screening phase 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.

11. Has positive test result(s) for alcohol and/or drugs of abuse (eg, barbiturates, methadone, opiates including methadone, cocaine, PCP, MDMA, and amphetamine/ methamphetamine) at screening or DB baseline.

    - 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 proceed with DB treatment.
    - 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 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 eligible.
    - Retesting is not permitted for positive test result(s), except for reasons stated above.

    Use of cannabinoids at frequency of up to once a week is allowed as long as the participant does not meet the criteria for moderate-to-severe substance use disorder.

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

    - Severe renal insufficiency (creatinine clearance <30 mL/min).
    - Clinically significant or unstable cardiovascular, respiratory, GI, 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 whose disease is considered controlled (HbA1c ≤9.0%) may be eligible to participate if otherwise medically healthy; if taking glucose-lowering medication(s) these must be on a stable regimen for at least 2 months prior to screening.

13. 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 TSH value out of range, a 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 preexisting 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.

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

15. Has significant medical illness, particularly an unstable medical problem (to be reviewed with the sponsor's Medical Monitor).

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

17. 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).

18. Has known allergies, hypersensitivity, intolerance, or contraindications to aticaprant and/or any of its excipients.

Prior/Concomitant Therapy

19. Has taken any prohibited therapies, as noted in Section 6.9.2 and Section 10.6 that would not permit dosing on Day 1 (ie, DB Baseline).

20. 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.

21. Ongoing psychological treatments (eg, Cognitive Behavior Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy), 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.

Prior/Concurrent Clinical Study Experience

22. Has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 60 days or 10 half-lives (for investigational drugs), whichever is longer, before the start of the screening phase or has participated in 2 or more clinical interventional studies for MDD or other psychiatric conditions (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

23. Criteria modified per Amendment 1

    23.1 Has history (prior to the start of the current MDE) of 1 or more of the following DSM-5 diagnoses:

    - Female sexual arousal/interest disorder, female orgasmic disorder, genito-pelvic pain/penetration disorder
    - Male hypoactive sexual desire disorder, erectile disorder, premature (early) ejaculation, and delayed ejaculation.

    Note: Per DSM-5 sexual dysfunction disorder requires ruling out problems that are better explained by a nonsexual mental disorder, by the effects of a substance (e.g., drug or medication like SSRI/SNRI), by a medical condition (e.g., due to pelvic nerve damage), or by severe relationship distress, partner violence, or other stressors.

24. Participant is a woman who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 1 month after the last dose of the study intervention.

25. Plans to father a child while enrolled in this study or within 90 days after the last dose of study intervention.

26. 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.

27. Participant is an 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 must ensure that all study enrollment criteria have been met at screening. 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 must be

excluded from participation in the study. Section 5.4 describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.2.11.

5.3. Lifestyle Considerations

Potential participants are recommended to follow these lifestyle restrictions during the study:

1. Should not consume food or beverages containing grapefruit juice, Seville oranges (including any orange marmalade), or quinine (eg, tonic water) and herbal products containing St. John's wort, ephedra, ginkgo, ginseng, or kava from 1 week before the first dose of study intervention and throughout the duration of the DB Treatment Phase until the last dose of study intervention in that phase.

2. The use of limited amounts of alcohol (up to 2 standard drinks 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% 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).

3. Participants should be advised not to donate blood during the study and for at least 3 months after completion (ie, final follow-up visit) 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. This study will use IWRS. When available, the investigator may generate screening and enrollment logs directly from 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. In cases where the participant is not enrolled into the study, the date seen and age at initial informed consent will be used.

If a participant is a screen failure but in the future is expected to meet the eligibility criteria, the participant may be rescreened on one occasion only. This should be discussed with and approved by the sponsor's Medical Monitor or designee prior to rescreening. Rescreened participants must be assigned new participant number, undergo the informed consent process, and then restart a new Screening Phase. Participants who failed screening on DSM-5 criteria for MDD cannot be rescreened. The sponsor will evaluate and approve/reject requests to rescreen an individual participant on a case-by-case basis.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention

Not applicable for this study.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Aticaprant/JNJ-67953964

Authorization status in the EU/EEA:

<table><tr><td>Authorized</td><td>-</td></tr><tr><td>Unauthorized
Unauthorized</td><td>Aticaprant/JNJ-67953964
Matching placebo</td></tr></table></td></tr>
<tr><td>AxMP</td><td>Current SSRI/SNRI antidepressant*

Authorization status in the EU/EEA:

<table><tr><td>Authorized</td><td>citalopram
duloxetine
escitalopram
fluvoxamine
fluoxetine
milnacipran
levomilnacipran
paroxetine
sertraline
venlafaxine
desvenlafaxine</td></tr><tr><td>Unauthorized</td><td>-</td></tr></table>The AxMPs will be used in accordance with the terms of their marketing authorization as described in the applicable local prescribing information.</td></tr>
</table>

* Permitted SSRIs/SNRIs are listed.

The description of the study intervention (aticaprant 10 mg or placebo) is provided in the table below. Study intervention administration must be captured in the source documents and the CRF. Study site personnel will instruct participants on how to store study intervention for at-home use as indicated for this protocol. A participant diary to capture the current SSRI/SNRI antidepressant therapy during Screening and DB Treatment Phases (one only, the AxMP during the DB Treatment Phase) and the study intervention during the DB and OL Treatment Phases will be provided.

Aticaprant will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

In the DB Treatment Phase all participants will continue their current SSRI/SNRI antidepressant therapy at the same dose without change, which will be taken around the same time of the day as prior to entering the screening phase. During OL Treatment Phase, changes to the current antidepressant therapy are allowed (per investigator's discretion).

If appropriate, additional details about the study intervention may be provided in a pharmacy manual/study site IP manual that is provided separately and noted in Section 8.

Description of Interventions

Group/Arm Name	DB Treatment Phase (randomized to adjunctive aticaprant) and OL Treatment Phase	DB Treatment Phase (randomized to adjunctive placebo)
Intervention Name[a]	Aticaprant/JNJ-67953964	Placebo
Type	Drug	Drug
Dose Formulation	Film-coated tablet	Matching placebo tablet
Unit Dose Strength(s)	10 mg per tablet	Matching placebo tablet
Dosage Level(s)	10 mg (1 tablet) once daily preferably in morning	1 tablet once daily preferably in morning
Route of Administration	Oral	Oral
Use	Experimental	Placebo-comparator
Investigational Medicinal Product (IMP)	Yes	Yes
Non-Investigational Medicinal Product/ Auxiliary Medicinal Product (NIMP/AxMP)	No	No
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling (Labels will contain information to meet the applicable regulatory requirements.)	Individual participant blister kits[b] Child resistant	Individual participant blister kits[b] Child resistant
Food/Fasting Requirement	With or without food	With or without food

[a] The study intervention will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

[b] Otherwise described as "container" throughout the document.

6.2. Preparation/Handling/Storage/Accountability

In this section the term "study intervention" refers to the IMP (aticaprant 10 mg or placebo).

Preparation/Handling/Storage

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

Refer to the pharmacy manual/study site investigational product and procedures manual for additional guidance on study intervention preparation, handling, and storage.

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. Whenever a participant brings his or her study intervention to the study site for pill count, this is not seen as a return of supplies. 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 interventions are provided in the study site IP manual.

6.3. Assignment to Study Intervention

In this section the term “study intervention” refers to the IMP (aticaprant 10 mg or placebo).

Intervention Allocation

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

6.4. Blinding, Masking

In this section the term “study intervention” refers to the IMP (aticaprant 10 mg or placebo).

Participants will be randomized to receive aticaprant 10 mg or placebo. The study intervention will be administered orally as 1 film-coated tablet, 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, intervention allocation, and biomarker) 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 for the unblinding must be documented in the IWRS, and reason for the unblinding must be documented in the appropriate section of the CRF 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 will discontinue their study intervention from the DB Treatment Phase and should return for follow-up assessments as indicated in Section 4.1.3. Participants who have discontinued study intervention during the DB Treatment Phase are not eligible for participation in the OL Treatment Phase.

In rare circumstances when a potential safety issue that may impact the overall benefit-risk assessment of the investigational product has been identified in this study, selected Sponsor personnel may be unblinded to safety-related data in order to investigate the safety issue and determine if additional actions are required. The safety data should be kept blinded to any personnel not essential to the safety review.

If other rare, unforeseen circumstances arise that may necessitate unblinding of selected Sponsor personnel, these will be assessed and documented on a case-by-case basis. The data should be kept blinded to any personnel not essential to the review or investigation.

6.5. Study Intervention Compliance

Except for on-site clinic visits, the study intervention will be self-administered by participant at home once 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 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 6 weeks of 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, etc) 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.

6.6. Dose Modification

This is a fixed dose study of adjunctive aticaprant 10 mg once daily or adjunctive placebo once daily. No dose modifications in study intervention are permitted during the DB Treatment Phase. In the OL Treatment Phase, no dose modifications are permitted for aticaprant 10 mg. Changes to the current antidepressant therapy are allowed (per investigator’s discretion) in the OL Treatment Phase.

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

Participants will be instructed that aticaprant will not be made available to them after they have completed the OL Treatment Phase (Week 31). Further clinical/standard-of-care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician.

6.8. Treatment of Overdose

For this study, any dose of aticaprant greater than 30 mg (3 tablets) 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 CRF as an AE.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

6.9. Prior and Concomitant Therapy

Prestudy non-antidepressant therapies administered 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 CCI [redacted], must be recorded (eg, dose, duration, reason) in the "Concomitant Therapy" CRF. Similarly, for POCBP oral contraceptives or hormonal replacement therapies ongoing or initiated/changed during the study should be recorded in the concomitant therapy CRF.

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 nonpharmacological treatments (eg, psychotherapy, transcranial magnetic stimulation). 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" CRF.

Concomitant therapies must be recorded throughout the study, beginning with signing of the ICF and continuing up to the last study visit. For participants who fail screening, concomitant therapies do not need to be recorded unless there is an AE.

Recorded information will include a description of the type of therapy, duration of use, dosing regimen, route of administration, and indication. Information on concomitant therapies should also be recorded 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 6.9.2 and Section 10.6 should be taken into account.

Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study. Tapering and discontinuation of prohibited therapies should be initiated after completion of the SIQA and confirmation that this was passed:

- Participants taking antidepressant medications at screening which are not listed on the MGH ATRQ (for a complete list of antidepressant medications, please refer to Section 10.6 for a list of medications used for the treatment of depression) 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, including medications taken for reasons other than depression (eg, insomnia or anxiety) will be tapered (if applicable) and discontinued during the screening phase, per the local prescribing information or clinical judgment.

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. If any vaccines (COVID-19 or other vaccines, eg, influenza) are administered, these should be recorded in the source documents and entered in the CRF.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as psychotherapy, electrical stimulation, acupuncture, special diets, exercise regimens) different from the study intervention must be recorded in the CRF.

6.9.1. Current (SSRI/SNRI) Antidepressant Therapy

Throughout the Screening and DB Treatment Phases, all participants will need to continue their current SSRI/SNRI antidepressant therapy **(one only)** at the same dose without change, which will be taken around 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. Participants will only continue one of these allowed antidepressants at an adequate and tolerated dose (which is within the approved range for the relevant antidepressant) during the study. Other antidepressants and any medications listed on the MGH-ATRQ taken in addition to the current SSRI or SNRI, including for reasons other than depression (eg, insomnia or anxiety) will be tapered (if applicable) after completion of the SIQA and confirmation that this was passed, and discontinued prior to the first dose of study intervention. No changes in current antidepressant or dose are permitted from screening until the end of the DB Treatment Phase.

Throughout the OL Treatment Phase, participants will receive adjunctive aticaprant along with their standard-of-care antidepressant therapy. It is recommended that participants continue the same SSRI/SNRI antidepressant therapy taken during the DB Treatment Phase. Changes to the

current antidepressant therapy are allowed (per investigator's discretion) in the OL Treatment Phase as long as the reason is documented in the participant's source documents and eCRF.

The participant's current SSRI/SNRI antidepressant therapy 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.

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 instructions 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). During the DB Treatment Phase, compliance to the SSRI or SNRI (the one that is continued in these phases) will be assessed by documented records (medical/pharmacy/prescription records, pill counts, etc). In the 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 in the Screening and DB Treatment Phases (one only, the AxMP, during the DB Treatment Phase) (see Section 1.3).

6.9.2. Prohibited Therapies

A list of prohibited concomitant therapies is provided in Section 10.6. 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.

The prohibited medications listed in Section 10.6 and pharmacological and nonpharmacological therapies used to treat SDF are prohibited from 1 week prior to the first dose of study intervention in the DB Treatment Phase until after the last dose of study intervention in the DB Treatment Phase.

Aticaprant is primarily metabolized by CCI Participants are recommended to not use medications that are strong or moderate CCI inhibitors or inducers or dual inhibitor/inducer of CCI and if their use is necessary, the sponsor's Medical Monitor should be consulted. See Section 10.6 for a listing of examples of such medications.

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

Participants receiving psychotherapy (including cognitive behavioral therapy; CBT), can continue receiving psychotherapy. New psychotherapy or changes to the ongoing psychotherapy is allowed during the OL Treatment Phase of the study. Any change in existing therapy or new psychotherapy

must be documented on the concomitant therapies form. New psychotherapy or changes to the ongoing psychotherapy are not allowed during the DB Treatment Phase.

Magnetic and electrical stimulation therapies: electroconvulsive therapy, vagal nerve stimulation, deep brain stimulations, transcranial magnetic stimulation of any type, or direct current stimulation or electrical stimulation are prohibited from screening until the last study visit.

Note: Use of cannabinoids at frequency of up to once a week is allowed as long as the participant does not meet the criteria for moderate-to-severe substance use disorder.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

All participants who prematurely discontinue study intervention during the DB Treatment Phase or OL Treatment Phase will have an EOT/EW Visit (Visit 2.6 or Visit 3.7 in the SoA, see Section 1.3) and a Follow-up Phase (Visit 4.1 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 or OL Treatment Phase.

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

- The participant withdraws consent to receive study intervention.
- 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 10.4.
- Noncompliance with study intervention administration (to be assessed on a case-by-case basis).
- 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.

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 2.6) 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 4.1). Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant.

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

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 10.5, 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 average QTcF of three 12-lead ECGs, recorded 4 minutes apart will be used to assess QTc stopping criteria. The QTc stopping criteria procedure applies to any on-treatment 12-lead ECG.

A participant who meets either of the following criteria (after baseline, Day 1, pre-randomization) based on the average of triplicate ECG readings (see Section 8.3.3) 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 Discontinuation

CCI

CCI

[redacted]

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 study completion, the reason for withdrawal is to be documented in the CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed. Participants who withdraw will not be replaced.

With the exception of participants who withdraw consent, participants who are withdrawn from the study will have an EW visit and then enter the Follow-up Phase of the study. If the EW visit occurs on the same day as a scheduled visit, the EW visit can be performed on the same day and duplicate assessments are not required.

Withdrawal of Consent

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the CRF 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 EW visit and the Follow-up Phase. 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). Participants who wish to withdraw from the study should be asked if they are agreeable to continue to an EW visit 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 study with the reason noted as "Other"

and will specify the reason why. For a participant who does select "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 IRB/IEC.

Managing Missing Data in the DB Treatment Phase

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 2.6) 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 4.1).

Participants that discontinue study intervention early (ie, prior to completion of the Day 43 Visit) or who are noncompliant 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 6.5) may not be eligible to continue in the OL Treatment Phase.

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 or inconvenience. To reduce missing data in this study, if a participant discontinues the study intervention for reasons other than withdrawal of consent, he/she will be expected to complete the Follow-up Phase (Visit 4.1).

Managing Missing Data in the OL Treatment Phase

If a participant discontinues from the study in the OL Treatment Phase an EOT/EW Visit (Visit 3.7) 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 4.1).

To reduce missing data in this study, if a participant discontinues the study intervention for reasons other than withdrawal of consent, he/she will be expected to complete the Follow-up Phase (Visit 4.1).

7.2.1. Withdrawal From the Use of Study Samples

Withdrawal From the Use of Study Samples

The participant may withdraw consent for use of study samples, including study samples, for research. In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of sample retention are presented in the ICF(s).

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 at time of enrollment.

In addition, the study site should emphasize the importance of follow-up information to the participant at time of enrollment.

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 and in the CRF.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

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

Order of Assessments

Site-based MADRS assessments will be performed by qualified raters either using videoconferencing, which provides the opportunity to schedule and complete the MADRS assessment before or after the on-site visit but respecting the visit window, or face-to-face at the site.

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 assessments (see Section 10.7) and further details are provided in a separate manual provided to the site (see below in Study-Specific Materials). When possible, 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 (MADRS [SIGMA version]), if not completed via videoconference, before the actual visit, CGI-S, C-SSRS, and other safety assessments.
- Twelve-lead ECG readings will be performed at the time points specified in the SoA. 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.

At baseline it is recommended that MADRS assessment and review of inclusion and exclusion criteria are done first to confirm eligibility of patient prior to other safety and PRO assessments.

The total blood volume to be collected from each participant will be approximately 76 mL. Refer to the table below.

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	6	27.0
- TSH/FT_4	2.5	1	2.5
- Lipid Panel	2.5	1	2.5
Efficacy			
Pharmacokinetic samples	4.0	1	4.0
Biomarker samples (plasma and serum)	20.0	2	40.0
Approximate Total[c]		11	76.0

Abbreviations: FT_4=free thyroxine; HbA1c=Hemoglobin A1c; 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.
c. 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.

Remote Contact Visits

Remote contact visits (ie, telemedicine visits, conducted via phone or video conference) will be implemented in this study (see Section 1.3).

The following study procedures may be performed during remote contact visits: MADRS (Site Rater, SIGMA version), CCI CGI-S (depression), CCI PHQ-9, CCI CSFQ-14, CCI C-SSRS, menstrual cycle tracking, review of concomitant therapy, and review of AEs (see Section 1.3).

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 (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
- IP Binder, including the IP Procedures Manual
- Laboratory manual and materials
- Guidance on the recommended order of study procedures
- 12-lead ECG equipment and associated materials (eg, manual)
- Clinician-administered and PRO assessments:
  - Paper versions, as applicable
  - Electronic devices and associated materials
- Procedural documents for SIQA
- Procedural documents for independent remote rater and site-based rater interviews
- CRF Completion Guidelines
- Sample ICF
- IWRS manual
- Participant recruitment materials
- Participant diaries
- Study guide for Participant Experience Interview and associated Participant Interview Manual. Interviews will be conducted by a third-party vendor, if applicable.
- Engage: A Smartphone Application used for video and audio teleconferencing
- The Engage application does not place cookies on the participant's device or provisioned 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 is captured on the vendor's conduit server only.

8.1. Administrative and General/Screening Procedures

The assessments in the following sections are performed only during the screening phase. Assessments will be performed by appropriately trained and certified investigators or designees.

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

The SCID-CT is a semi-structured interview guide for making the major DSM-5 diagnoses. It is administered by a clinician or trained mental healthcare professional who is familiar with the DSM-5 classification and diagnostic criteria as well as clinical diagnostics.

8.1.2. 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 MDE. 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/rater in collaboration with the participant.

8.1.3. Site Independent Qualification Assessment (SIQA)

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

8.2. Efficacy Assessments

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

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

The 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 one another.

8.2.1. 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 (Montgomery 1979). The scale consists of 10 items, each of which is scored from 0 (item not

present or normal) to 6 (severe or continuous presence of the symptoms), 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 qualified site-based raters via video teleconferencing or face-to-face at the site during the study using the MADRS (SIGMA version) (see Section 8 for additional details). The typical recall period for the MADRS is 7 days. To minimize the risk of unblinding the treatment assignment, raters performing efficacy assessments will be different from those performing safety assessments; clinicians who perform the MADRS assessments will not be involved in assessing AEs. MADRS assessments may be audio recorded for the purpose of quality monitoring.

8.2.2. Snaith-Hamilton Pleasure Scale (SHAPS)

The SHAPS (Nakonezny 2010; Snaith 1995) is a self-reported, 14-item instrument, developed for the assessment of hedonic capacity. It has excellent internal consistency, with construct validity, and is unidimensional in assessing hedonic capacity among adult patients with MDD. The SHAPS possesses excellent psychometric properties, is not influenced by participant demographic and clinical characteristics, and is appropriate for use in both clinical and research settings.

Participants score whether they experience pleasure in performing a list of activities or experiences over the "past few days." Participants can rate the answers as "definitely/strongly agree," "agree," "disagree" or "strongly disagree." Answers will be rated according to (Franken 2007): "Definitely agree" will be rated 1, "Agree" will be rated 2, "Disagree" will be rated 3, and "Definitely disagree" will be rated 4. So, the score of the scale will range from 14 to 56. The mean score in a population of patients hospitalized for treatment of depression was 34.4 (Franken 2007).

8.2.3. CCI)

CCI [redacted]

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

The CGI-S (depression) provides an overall clinician-determined summary measure of the severity of the participant's illness that takes into account all available information, including knowledge of the participant's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the participant's ability to function (Guy 1976). The CGI-S evaluates the severity

of psychopathology on a scale of 0 to 7. Considering total clinical experience, a participant is assessed on severity of mental illness at the time of rating according to: 0=not assessed; 1=normal (not at all ill); 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients. The CGI-S permits a global evaluation of the participant's condition at a given time. To minimize the risk of unblinding the treatment assignment, raters performing efficacy assessments will be different from those performing safety assessments; clinicians who perform the CGI-S assessments will not be involved in assessing AEs.

8.2.5. CCI

CCI [redacted]

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

The PHQ-9 scale scores each of the 9 symptom domains of the DSM-5 MDD criteria and it has been used both as a screening tool and a measure of response to treatment for depression (Spitzer 1999). Each item is rated on a 4-point scale (0=not at all, 1=several days, 2=more than half the days, and 3=nearly every day). The participant's item responses are summed to provide a total score (range of 0 to 27), with higher scores indicating greater severity of depressive symptoms. The recall period is 2 weeks.

8.2.7. Changes in Sexual Function Questionnaire (CSFQ-14)

The CSFQ-14 was developed and validated to assess treatment-emergent sexual dysfunction in MDD patient populations. There are separate versions for males and females. The scale uses 5-point Likert-response options to provide the patient an opportunity to self-evaluate his or her sexual behaviors or problems in a number of areas. The CSFQ-14 recall period used in this study is the "past two weeks." For all items, higher scores reflect higher sexual functioning (Keller 2006). For 12 of the 14 items, higher sexual functioning corresponds to greater frequency or enjoyment/pleasure (eg, 1=never to 5=every day). For 2 items (item 10, assessing loss of interest after arousal for women and priapism for men, and item 14, assessing painful orgasm), higher sexual functioning corresponds to lower frequency (eg, 1=every day to 5=never). Items 10 and 14 are included in the total score but not in any subscale score. CCI [redacted] Normal SF is defined as a CSFQ-14 total score at DB Baseline of >41 for female and >47 for male participants. The response time for the CSFQ-14 is between 4 and 5 minutes.

8.2.8. CCI

CCI [redacted]

CCI [redacted]

8.2.9. CCI [redacted]

CCI [redacted]

8.2.10. CCI [redacted]

CCI [redacted]

8.3. Safety Assessments

An IDMC will be commissioned to periodically review safety data. Details regarding the IDMC are provided in Section 10.2.7.

Physical examinations, body weight, BMI, vital signs (including blood pressure, pulse/heart rate, and temperature measurements), 12-lead ECGs, clinical laboratory tests (including hematology, serum chemistry, and urinalysis), and 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.

AEs, including TEAEs, will be evaluated throughout the course of the study. Clinically relevant treatment-emergent AESIs will be examined separately and grouped in categories as defined by the Standardized MedDRA (version 23.0, or above if applicable).

AEs will be reported and followed by the investigator as specified in Section 8.4 and Section 10.3.

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

Any clinically significant abnormalities persisting at the end of the study/EW will be followed by the investigator until resolution or until a clinically stable condition is reached.

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

8.3.1. 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 neurologic 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.

8.3.2. 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.

8.3.3. 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 DB baseline (Day 1, pre-randomization) until 4 regular consecutive complexes are available in good readable quality.

Note:

- 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 medical stability for inclusion (during screening and baseline) and for QTc stopping criteria during the treatment phases (see Section 7.1.2).

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: ECG(s), vital signs, blood draw.

8.3.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology and urine samples for urinalysis will be collected as noted in Section 10.1. 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.

Clinical laboratory assessments, including TSH (all participants, at screening only), FSH (female participants only, at screening only if required for documentation that a female participant is not of childbearing potential, see Section 10.4), FT_4, hematology, serum chemistry, HbA1c, lipid panel, and urinalysis that should be performed at approximately the same time throughout the study. During screening, the lipid panel must be performed under fasting conditions.

8.3.5. Pregnancy Testing

For female participants of childbearing potential, 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 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.

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

Emergence of potential suicidal ideation will be assessed using the C-SSRS at screening, and at all subsequent study visits. The C-SSRS is a low-burden measure of the spectrum of suicidal ideation and behavior that was developed to assess severity and track suicidal events through any treatment (Posner 2007). It is a clinical interview providing a summary of both suicidal ideation and behavior that can be administered during any evaluation or risk assessment to identify the level and type of suicidality present. The C-SSRS has been used frequently in clinical studies, and is a validated, standard measure for suicidal ideation assessment.

Two versions of the C-SSRS will be used in this study, the Baseline/Screening version, and the Since Last Visit version. The Baseline/Screening version of the C-SSRS will be used at the screening visit. In this version, suicidal ideation will be assessed at 2 time points (“lifetime” and “in the past 3 months”) and suicidal behavior will be assessed at 2 time points (“lifetime” and “in the past 6 months”).

Sites should specify the date of C-SSRS suicidal ideation with intent or plan history within the past 3 months and/or suicidal behavior 6 months prior to screening in the CRF. Participants are excluded if they have serious suicidal ideation (corresponding to a positive response to C-SSRS item 4 or 5) within 3 months or suicidal behavior within 6 months prior to screening.

All subsequent C-SSRS assessments in this study will use the Since Last Visit version, which will assess suicidal ideation and behavior since the participant's last visit.

8.3.7. Menstrual Cycle Tracking

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

8.4. 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 designated representative) for the duration of the study.

Further details on AEs, SAEs, and PQCs can be found in Section 10.3.

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

All AEs

All AEs, including AESIs 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

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.

SAEs, 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.

A possible Hy's Law Case is defined by the occurrence of ALT or AST ≥3 x ULN, ALP <2 x ULN together with total bilirubin ≥2 x ULN (or at least doubling of direct bilirubin in known Gilbert's

syndrome) or 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 (ie, same reporting timelines and transmission path as SAEs), using the SAE form, even before all other possible causes of liver injury have been excluded.

Information regarding SAEs (initial and any follow-up) will be transmitted to the sponsor/CRO immediately, but no later than 24 hours of their knowledge of the event, using the study-specific Serious Adverse Event Form with the complete (eg, causality, narrative) information available in the medical records that has been already assessed by a study site physician, and transmitted via CRF through JEISR.

8.4.2. 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 systemic events for which the participant is specifically questioned (see Section 8.4.7).

Unsolicited Adverse Events

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

8.4.3. 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 or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

AEs and the special reporting situation of pregnancy will be followed by the investigator as specified in Section 10.3.

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

The sponsor assumes responsibility for appropriate reporting of the Safety Information to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all 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 (if it occurs in the DB Treatment Phase), 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 events 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.

8.4.5. 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 promptly be 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.

8.4.6. Disease-related Events and Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

All events that meet the definition of an SAE will be reported as SAEs, regardless of whether they are protocol-specific assessments.

8.4.7. 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 information on the CRF 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 10.3.3 for guidance on assessing the severity of an AESI.

Note: If the event meets the seriousness criteria (see Section 10.3.1), 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 10.3.5).

8.5. Pharmacokinetics

8.5.1. Evaluations

Venous blood sample of approximately 4 mL will be collected for measurement of plasma concentration of aticaprant and any relevant metabolite(s) (if warranted) will be collected from participants as indicated in the SoA (see Section 1.3, Clinical Pharmacology Assessments).

The exact date and time of PK blood sample collection must be recorded, along with all concomitant medications (dose, drug, start and stop date). Study intervention administration on the day before PK sample collection will be accurately recorded by exact dosing date and time by the participant in the participant diary. Plasma 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 biologic samples can be found in the laboratory manual.

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

Pharmacokinetic/Pharmacodynamic Evaluations

The relationship between efficacy endpoints such as MADRS or change in CSFQ-14 total score 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 MADRS or CSFQ-14 total score.

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

8.6. Pharmacodynamics

Not applicable.

8.7. Biomarkers

Blood samples will be collected as indicated in the SoA (see Section 1.3, Biomarkers Assessments) to explore biomarkers that help to explain interindividual variability in efficacy, PK, PD, 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, Biomarker Assessments).

Sample collection and testing will comply with local regulations.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Medical Resource Utilization and Health Economics

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

8.10. Participant Experience Interview (Optional)

An optional Participant Experience Interview may be conducted as a sub-study in consenting participants at study sites in select countries/territories. The sub-study is optional and choosing not to participate in the interview will not impact the participant's involvement in any other aspects of the main study. Participants randomized in the main study who have provided the sub-study specific separate informed consent may participate in the Participant Experience Interview. The opportunity to provide informed consent to participate in this sub-study may be offered once the participant's eligibility is confirmed and should be obtained prior to the interview.

The Participant Experience Interview will be conducted by a third-party vendor using interviewers trained in qualitative semi-structured interviewing. The objectives of this interview study are to better understand the participant experience during the clinical study, including the participant's experience with depression and anhedonia as well as to explore other patient-centered concepts such as sexual functioning. The interview will be conducted within approximately 7 days of the participant's scheduled DB EOT or EW Visit.

The interview will be conducted via telephone in the local language in accordance with local guidelines and will last approximately 60 minutes. The interview will follow a semi-structured interview guide using open-ended questions to guide discussion without leading. The interview will be audio recorded, transcribed, and analyzed. Only de-identified transcripts will be sent to the sponsor.

Further details can be found in the separate study guide for the Participant Experience Interview and associated Participant Interview Manual. The results from the Participant Experience Interviews will be analyzed and presented separately from the main study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done 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.

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. Analysis Sets

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

Analysis Sets	Description
Enrolled	All participants who sign the ICF
Randomized	All participants who were randomized in the study
Full Analysis Set (DB) – FAS (DB)	All randomized participants who took take at least 1 dose of the study intervention in the DB Treatment Phase
Full analysis Set-Sexual Functioning (DB) - FAS_SF (DB)	All randomized participants with SDF at DB baseline who take at least 1 dose of study intervention in the DB Treatment Phase
Safety (DB)	All randomized participants who take at least 1 dose of study intervention in the DB Treatment Phase.

The analyses of the primary endpoint and change of CCI total score will be based on FAS (DB), and change of CSFQ-14 total score will be based on FAS_SF (DB).

The safety analyses in the DB Treatment Phase will be based on the safety (DB) analysis set.

The analysis of efficacy and safety endpoints in the OL Treatment Phase and the corresponding analysis sets will be described in the Statistical Analysis Plan.

9.3. Statistical Analyses

The statistical analysis plan will be finalized prior to database lock and it 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.

9.3.1. General Considerations

All efficacy and safety analyses will be performed for each phase using analysis sets that are defined for these endpoints for the different phases. Further details will be provided in the SAP.

9.3.2. Primary Endpoint/Estimand Analysis

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

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: Patients with a diagnosis of MDD ANH+ who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI.

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 score as a covariate. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. In case of convergence problems with the default Newton Raphson algorithm, alternative approaches will be tried in the following order before using a structure variance-covariance matrix: Fisher scoring algorithm, and factor analytic structure. If the convergence issues persist with the unstructured variance-covariance matrix, alternative variance-covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and AR(1) with separate subject random effect. A robust sandwich variance estimator will be used if a structured covariance matrix is implemented. Comparison between aticaprant 10 mg and placebo at Day 43 will be performed using the appropriate contrast. Difference in least square means and 2-sided 95% CIs will be presented.

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

Justification of MMRM: CCI [redacted] 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.

9.3.3. Secondary Endpoints/Estimand Analysis

The following key secondary endpoints are defined in this study:

i. Change from baseline in CCI [redacted] total score at Day 43 in participants belonging to FAS (DB): The same estimand as described above (except the endpoint component) and corresponding analyses as for the primary endpoint will be used for this key secondary endpoint.

ii. Change from baseline in CSFQ-14 total score at Day 43 in participants belonging to FAS_SF (DB): Except for the components defined below, other components of the estimand are similar to those described for the primary endpoint:

Population: Patients with a diagnosis of MDD ANH+ with SDF who have had an inadequate response to current antidepressant therapy with an SSRI/SNRI.

Endpoint: Change in CSFQ-14 total score from baseline to Day 43.

Data will be analyzed using the same MMRM model as described for the primary endpoint, but the model will include an additional fixed term, sex. All other details of the analysis are similar to those for the primary 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 two-sided 0.05 level accounting for multiplicity due to the primary (MADRS total score) and the 2 key secondary efficacy endpoints (CCI [redacted] total score, and CSFQ-14 total score). The testing

procedure will first test the primary endpoint at two-sided 0.05 level. If the hypothesis corresponding to the primary endpoint is rejected, then the first key secondary endpoint (CCI total score) will be tested at 2- sided 0.05 level. If the hypothesis corresponding to the first key secondary endpoint is rejected, the testing will proceed to the second key secondary endpoint (CSFQ-14 total score) at 2- sided 0.05 level. If the hypothesis corresponding to the primary endpoint or the first key secondary endpoint is not rejected, then the testing procedure will stop, and the endpoint(s) further down the testing sequence will not be tested.

The analyses for the other efficacy endpoints will be described in the SAP. To evaluate the consistency of efficacy in subgroups of patients, 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.

9.3.4. Safety Analyses

All safety analyses in the DB and OL Treatment Phases will be conducted on the Safety Analysis Set defined for the respective phases.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the day of last dose, or any AE that is a consequence of a preexisting condition that has worsened since baseline is considered to be treatment-emergent. All reported [treatment-emergent] AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

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 or an SAE.

All reported treatment-emergent AEs, ie, AEs with onset during the DB or OL Treatment Phase, or AEs that are a consequence of a preexisting condition that has worsened since baseline, will be included in the analysis. For each treatment-emergent AE, and AESI (see Section 8.4.7), the percentage of participants who experience at least 1 occurrence of the given event will be summarized by study intervention for each phase. Serious adverse events (SAEs) will be summarized separately.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for any participants who die, who discontinue study intervention due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test and study intervention in each phase. Descriptive statistics will be calculated for each laboratory analyte at baseline for observed values

and changes from baseline at each scheduled time point for each phase.

Proportion of participants with markedly abnormal results (the criteria of which are specified in the SAP) will be presented for each analyte and study intervention group for each phase.

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 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 prespecified 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 for each phase. 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 for each phase. Changes in body weight and BMI will be summarized descriptively.

C-SSRS

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

9.3.5. Other Analyses

An IDMC will be commissioned for this study to periodically review safety data as noted in Committees Structure in 10.2.7.

9.3.5.1. Pharmacokinetic Analyses

If feasible, population PK analysis of plasma concentration-time data of aticaprant may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc) will be tested as potential covariates affecting PK parameters. Details on the results of this population PK analysis will be presented in a separate Clinical Pharmacology report.

All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. All participants and samples excluded from the analysis will be clearly documented in the study report.

Descriptive statistics, including arithmetic mean, SD, coefficient of variation, interquartile range, median, minimum, and maximum will be calculated for the plasma aticaprant concentrations.

Plasma aticaprant concentrations data available will be provided in listings for all participants.

9.3.5.2. Biomarkers Analyses

Laboratory data of 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.

Laboratory data of biomarker levels at baseline will be combined in multivariate models (biosignatures) that will be optimized based on 2 key criteria: CCI [redacted]

9.3.5.3. Pharmacokinetic/Pharmacodynamic Analyses

Blood samples are collected for determination of plasma concentrations of aticaprant as indicated in SoA. A population-based PK analysis using PK data from previous studies of aticaprant Phase 1 and Phase 2a studies may be performed and may include derivation of post hoc Bayesian estimates of aticaprant PK parameters. Available covariates will be included in the model as necessary. If performed, the results of population PK and PK-PD analyses will be reported separately, as appropriate.

9.3.5.4. Benefit-risk Analyses

Benefit-risk assessment for aticaprant as adjunctive therapy to an antidepressant (SSRI or SNRI) in participants with MDD ANH+ will be assessed using a structured framework approach. Benefit-risk assessment will be in the DB Treatment Phase. Benefits in the assessment will include endpoints for the symptoms of depression (eg, relapse, MADRS total score), symptoms of anhedonia (eg, CCI [redacted] total score) and SF (eg, CSFQ-14). Assessment of risk will include clinically meaningful AEs, including TEAEs and AESIs such as CCI [redacted] and AEs leading to discontinuation.

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 also 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. Interim Analysis/Analyses

Not applicable.

9.5. Sample Size Determination

Approximately 350 participants will be enrolled in the study. Participants entering the DB Treatment Phase will be randomized in a 1:1 ratio to adjunctive aticaprant 10 mg or adjunctive placebo. CCI [redacted] this sample size will provide 90% power for the comparison between aticaprant 10 mg and placebo for the primary efficacy endpoint, 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 CCI [redacted]

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: 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 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. A 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>Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Bicarbonate
BUN
Creatinine
Glucose (in fasting condition when possible)
AST/SGOT
ALT/SGPT
GGT</td><td>Total bilirubin and Direct bilirubin
Alkaline phosphatase
CPK
LDH
Uric acid
Calcium
Phosphate
Albumin
Total protein
Cholesterol (in fasting condition)
Triglycerides (in fasting condition)
Magnesium</td></tr>
<tr><td></td><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 5.

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

Potential Hy's law Case (ALT or AST) ≥3 x ULN, ALP <2 x ULN together with Tbili ≥2 x ULN (or at least doubling of direct bilirubin in known Gilbert's syndrome) or INR >1.5 [if measured] reporting requirements are defined in Section 8.4.1.</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 dipstick result is abnormal)</u>
Red blood cells
White blood cells
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td colspan="2">If dipstick 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 Laboratory Tests</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 Screen for drugs of abuse (eg, opiates [including methadone], cocaine, amphetamines, methamphetamines, PCP, barbiturates, or 3,4-methylenedioxymethamphetamine [MDMA]) and cannabinoids, cannabidiol [CBD]. Urine drug tests will be done by the site at screening, at baseline, and as indicated in the SoA. Additional urine drug tests may be conducted as needed per the investigator's judgment.

• In some countries/territories, 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 participants with a history of thyroid disease or any participant (regardless of thyroid history) if the TSH value is out of range 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.

• FSH (female participants only, at screening only if required for documentation that a female participant is not of childbearing potential, see Section 10.4).

• Hemoglobin A1c (HbA1c).

• Alcohol breath test (at screening, at baseline, and as indicated in the SoA. Additional alcohol breath tests may be conducted as needed per the investigator's judgment).</td></tr>
</table>

10.2. Appendix 2: Regulatory, Ethical, and Study Oversight Considerations

10.2.1. 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- or 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 PCC may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, LTMs, CTMs, and/or CROs who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with 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 subinvestigators
- Documentation of subinvestigator 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 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.

Note for substudy for Participant Experience Interview (Optional) data collection: If implemented in this study (only in select countries), approval 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.

10.2.2. Financial Disclosure

Investigators and subinvestigators 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.

10.2.3. Informed Consent Process

Each participant must give consent according to local requirements after the nature of the study has been fully explained. 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.

Note for substudy for Participant Experience Interview (Optional) data collection: If implemented in this study (only in select countries), participants may be asked for consent to participate in this optional research (where local regulations permit). Refusal to participate in the optional research will not result in ineligibility for the study. If signed, a copy of this ICF will be given to the participant.

10.2.4. Recruitment Strategy

Various resources will be developed to support trial awareness and provide information and education to potential participants about the trial and clinical trials in general. Materials may include informational brochures, advertisements, study guides, provider referral materials and advocacy group outreach.

10.2.5. 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.

10.2.6. Storage, Use, Transfer, and Retention of Data and Samples for Additional Future Research

Study samples will be coded or anonymized at all times in accordance with the informed consent and will not be labeled with personal identifiers.

Investigator and study site will only store, use, transfer and retain data and study samples in accordance with the informed consent and applicable law, and in accordance with any separate written agreement with sponsor. Other than what is specified in a separate written agreement with sponsor, study site and investigator shall not conduct or facilitate any research by a third party not required by the protocol (i) on participants if such research interferes with the conduct of the study or (ii) on samples collected from study participants during the study if the research relates to aticaprant or (iii) on data collected from study participants during the study if the research relates to aticaprant.

Sponsor may store, use, transfer or retain the data and study samples for uses not specified by the protocol, including compatible research, in compliance with the informed consent and applicable law.

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).

10.2.7. Committees Structure

Data Monitoring Committee

An IDMC will be established to periodically review safety data. After the review, the IDMC will make recommendations regarding the continuation of the study. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter.

10.2.8. Use of Information and Publication

All information, including but not limited to information regarding aticaprant, supplied by the sponsor to the study site or investigator and not previously published, and any data or analysis generated as a result of this study, are considered confidential and remain the sole property of the sponsor. Study site and investigator shall not use this information except in the performance of this study and shall not disclose this information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

Study site and investigator shall not publish study results except as required by law or as specified in a separate, written agreement between the sponsor and the study site or investigator.

The Sponsor will register the study and publish the study results in compliance with applicable law and may register the study or publish study results when not required.

Authorship of any peer-reviewed publications will be determined by mutual agreement in line with International Committee of Medical Journal Editors authorship guidelines.

In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the interim results of clinical studies as required by law.

For studies conducted in the EU under Regulation EU 536/2014 appropriate provisions for interim analyses should always be described in the protocol. Use one of the options below as appropriate. Other options might be considered in specific situations.

The disclosure of the study results will be performed after the end of study.

10.2.9. 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, 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 CRF 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 the data sources.

10.2.10. 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 CRF. All CRF 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 CRF are accurate and correct.

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

Data must be entered into the CRF in English. The CRF 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 a CRF are needed after the initial entry into the CRF, 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.

10.2.11. 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 the assessment by the investigator 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 CRF and will be considered source data

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

The minimum source documentation requirements for Section 5.1 and Section 5.2 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 or
- 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 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 CRF in the protocol include the eSource system but information collected through eSource may not be limited to that found in the CRF. 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.

10.2.12. Monitoring

The sponsor will use a combination of monitoring techniques 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. 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.

10.2.13. 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.

10.2.14. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP 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. For trials performed under Regulation [EU] No. 536/2014, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.

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.

10.2.15. Study and Site Start and Closure

First Act of Recruitment

The first subject 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

10.3. Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 on 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 8.4.1, 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).

10.3.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is assessed by the Investigator and documented in the Medical Records.

The assessment of causality must consider the following factors:

- Temporal relationship
- Clinical characteristics of event
- Pharmacological plausibility
- Confounding risk factors:
  - Concomitant medication
  - Underlying/concurrent disease
  - Family/social history
- Challenge:
  - De-challenge: Did the reaction improve when the investigational product was withdrawn, in the absence of any other treatment?
  - Re-challenge: What happens if participant is re-challenged with investigational product?
- Other considerations: Participant characteristics and past medical history, and quality of information

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.

10.3.3. 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).

CCI

[redacted]

CCI

[redacted]

10.3.4. 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

Participant-specific special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF.

10.3.5. 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 an SAE reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor immediately, but no later than within 24 hours of their knowledge of the event. The initial and follow-up reports of an SAE should be

transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

Information regarding SAEs (initial and any follow up) will be transmitted to the sponsor/CRO immediately, but no later than 24 hours of their knowledge of the event, using the study-specific Serious Adverse Event Form with the complete (eg, causality, narrative) information available in the medical records that has been already assessed by a study site physician, and transmitted via CRF through JEISR.

10.3.6. Product Quality Complaint Handling

Definition

A product quality complaint (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.

10.3.7. 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.

10.4. Appendix 4: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.4.5 and Section 10.3.

Definitions

Female Participants of Childbearing Potential

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

Female Participants 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 in the postmenopausal range (based on the central laboratory) 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 they wish 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 participant 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 ³1% 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
• Cap, diaphragm, or sponge with spermicide[b]
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)
• 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).

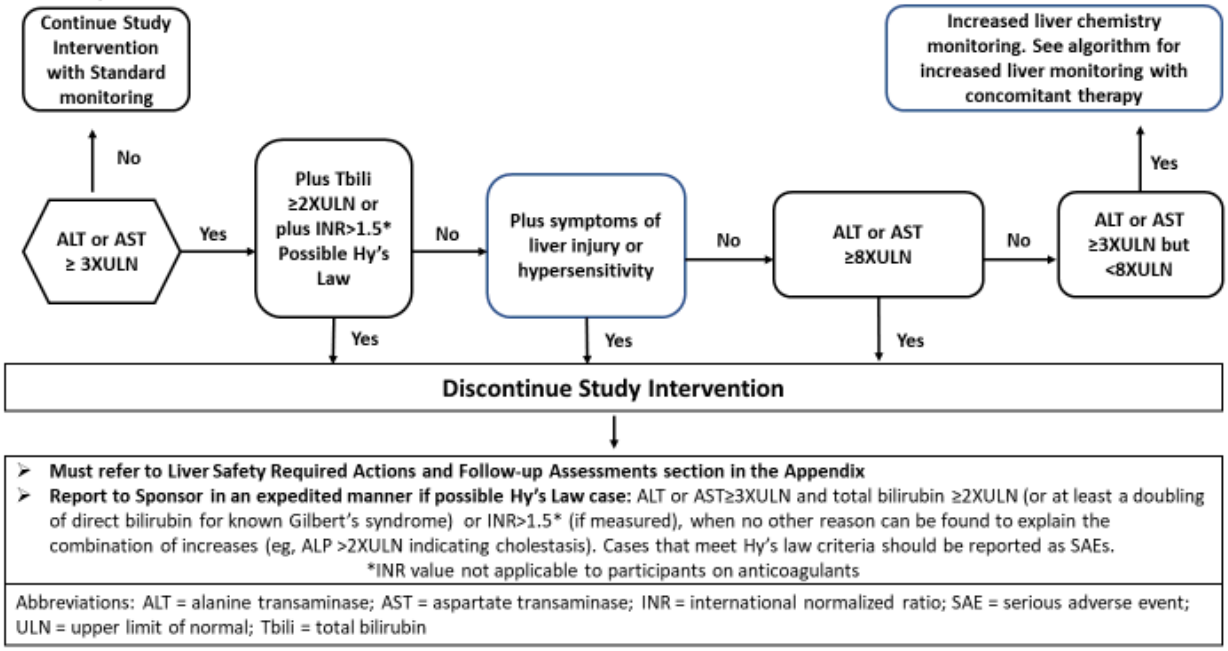
10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

10.5.1. Stopping Algorithm

10.5.1.1. ALT or AST

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

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



10.5.2. Follow-up Assessments

10.5.2.1. 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 10.5.1. • 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

10.6. Appendix 6: 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 prior to the first dose of study intervention in the DB Treatment Phase until after the last dose of study intervention in the DB Treatment Phase.

Note: If a medication is part of the antidepressant treatment regimen being taken at the time of signing the ICF (ie, start of screening phase), it must be continued unchanged until the SIQA confirmation of participant's eligibility; therefore, in such cases this requirement is not applicable until following the SIQA confirmation. In such cases the investigator may choose to taper the relevant medication during the up to 3-week taper period based on their clinical judgment.

Of note, for any concomitant medication that is not listed below but has the potential to be a strong CCI [redacted], please check with the sponsor's Medical Monitor.

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
ADHD medications (eg, atomoxetine, dexmethylphenidate, dexamphetamine, viloxazine guanfacine)	N	N	See also "Psychostimulants" row.	CCI [redacted]
Agomelatine	N	N		
Amantadine	N	N		
Amitifadine	N	N		
Antibiotics: Macrolides	Y	N	Episodic use allowed after consultation with sponsor's Medical Monitor	
Antibiotics: Nafcillin	Y	N		
Antibiotics: Quinolones	Y	N		
Anorexiants (eg, phentermine, phendimetrazine)	N	N		
Anticholinesterase Inhibitors	N	N		Participant population is excluded
Anticonvulsants	Y	Y	- Participants with uncontrolled (current or past 6 months) seizures are excluded. - Anticonvulsants with strong CCI [redacted] and/or CCI [redacted] induction potential (eg, CCI [redacted]	CCI [redacted]

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
			CCI are excluded. - Others with CCI and CC inhibition potential, used for other indication than MDD and limited period, are allowed. Consult with Medical Monitor before use. - Use as adjunctive treatment for MDD is prohibited.	
Antidepressants (*other than the specific antidepressant monotherapies listed in inclusion criteria of the protocol*) and medications used for treatment of depression (eg, S-adenosyl methionine ([SAMe])	N	N	- Only one of the oral antidepressant treatment options (listed in Section Inclusion Criteria) is permitted (if participant is taking more than 1 antidepressant from protocol-specified options, participant must be on monotherapy by-first dose of study intervention). - If a participant is taking a 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 one of the SSRI/SNRI options listed in protocol) is not permitted during the treatment phases.	CCI
Antifungals	N	N	Topical antifungals (like terbinafine) are allowed on a case-by-case assessment in consultation with sponsor's Medical Monitor.	
Antipsychotics	N	N	- Injectable long-acting antipsychotics	

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
			are prohibited from 1 injection cycle prior to first dose of study intervention.	CCI [redacted]
Antivirals: NNRTI	N	N		
Antivirals: Protease Inhibitors	N	N		
Appetite Suppressants (eg, ephedrine)	Y	N		
Aprepitant	N	N		
Avasimibe	N	N		
Barbiturates	N	N		
Benzodiazepines (at dosages equal to or less than the equivalent of 4 mg/day lorazepam) and non-benzodiazepine sleeping medication (including zolpidem, zaleplon, eszopiclone, and ramelteon)	Y	Y	- Participants taking these medications at study entry can continue these medications. - No dose increases "beyond the equivalent of 4 mg/day of lorazepam" or new benzodiazepine medications are permitted during screening and DB Treatment Phase.	
Benztropine	Y	N		
Bosentan	N	N		
Buspirone	N	N		
Chloral hydrate, melatonin, valerian	N	N		
Clonidine	N	Y	Continuous use for blood pressure control is allowed.	
Conivaptan	N	N		
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.	
Crizotinib	N	N		

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
Dopamine Receptor Agonists (not listed elsewhere)	N	N		CCI [redacted]
Dextromethorphan	N	N	Episodic use can be discussed on a case-by-case basis with sponsor's Medical Monitor.	
Glutamatergic Agents (ketamine, esketamine)	N	N	Episodic use (eg, anesthesia) can be discussed on a case-by-case basis with sponsor's Medical Monitor.	
Imatinib	N	N		
Methyldopa	N	N		
Metyrosine	N	N		
Memantine	N	N		
MAOIs	N	N		
Mood Stabilizing Agents (eg, lithium)	N	N		
Norepinephrine and dopamine reuptake inhibitors (eg, bupropion)	N	N		
Opioids	N	N	Brief treatment with opiates (eg for treatment of acute injuries, etc) can be discussed on a case-by-case basis with sponsor's medical monitor	
Opioid Receptor Agonists or Antagonists	N	N		
Psychostimulants (eg, amphetamines, methylphenidate, modafinil, armodafinil)	N	N		
Psychedelics (eg, psilocybin)	N	N		
Reserpine	N	N		
Scopolamine	N	N		
St. John's Wort	N	N		
Thyroxine/triiodothyronine (T3), thyroid hormone prescribed for depression	N	N		
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 screening.	

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
Trazodone	N	N	Not allowed even if used for other indications (eg, for sleep).	CCI [redacted]

Abbreviations: ADHD: attention deficit hyperactivity disorder; IM: intramuscular; IV: intravenous; MAOI: monoamine oxidase inhibitor; MDD: major depressive disorder; N: Prohibited; NNRTI: non-nucleoside reverse transcriptase inhibitor; PD: pharmacodynamics; PK: pharmacokinetics; 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.

10.7. Appendix 7: 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.”

10.8. Appendix 8: Study Conduct During a Major Disruption/ Pandemic

It is recognized that a major disruption/pandemic (eg, COVID-19) may have an impact on the conduct of this clinical study due to, for example, isolation or quarantine of participants and study site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being unavailable, isolated, or reassigned to critical tasks.

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 travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of a major disruption/pandemic scheduled visits cannot be conducted in person at the study site, they 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 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 "Major Disruption-related" or "Pandemic-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. Modifications made to the study conduct as a result of the major disruption should be summarized in the CSR.

If the participant has tested positive during a pandemic (eg, for COVID-19), the investigator should contact the sponsor's responsible medical officer to discuss plans for administration of study intervention, performing study assessments, and follow-up. Modifications made to the study conduct as a result of a pandemic should be summarized in the CSR.

10.9. Appendix 9: Protocol Amendment History

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

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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

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	19-Jun-2024 20:00:43 (GMT)	Document Approval