**Janssen Research & Development ***

**Clinical Protocol**

**Protocol Title**

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

**VENTURA-5**

**Short Title**

**A Study of Oral Aticaprant Plus an Oral Antidepressant to Prevent Return of Depression Symptoms in Participants With Major Depressive Disorder Who Experience a Loss of Interest and Pleasure as Part of Their Depressive Episode**

**Protocol 67953964MDD3005; Phase 3**
**Version: Amendment 1**

**JNJ-67953964 (aticaprant)**

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**Regulatory Agency Identifier Number(s):**
**IND:** 111006
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**Status:** Approved
**Date:** 27 June 2024
**Prepared by:** Janssen Research & Development, LLC
**EDMS number:** EDMS-RIM-1067875, 3.0

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

## PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | | |
|---|---|---|
| **Document** | **Country/Territory Affected** | **Date** |
| Amendment 1 | All | 27 June 2024 |
| Original Protocol | All | 18 March 2024 |

### Amendment 1 (27 June 2024)

**Overall Rationale for the Amendment:** The primary reason for this amendment is to remove inclusion criterion 20 to improve recruitment.

The changes made to the clinical protocol 67953964MDD3005 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 |
|---|---|---|
| 5.1 Inclusion Criteria | Removed criterion #20. | Criterion deleted in order to improve recruitment. |
| 1.1 Synopsis<br>9.3.2 Primary Endpoint/Estimand Analysis | Added “unstratified” to “The primary analysis of study intervention differences will be conducted using a log-rank test”. | Added to align with the feedback received from a major Health Authority. |
| 1.1 Synopsis<br>9.4 Interim Analysis | Added “in stable responders” to “The IA will be performed after approximately a total of 60 relapse events (of the 127 maximum) are observed”. | Added to align with the feedback received from a major Health Authority. |
| 1.3.1 Schedule of Activities During the Screening and Open-Label Treatment Phases<br>1.3.2 Schedule of Activities During the Double-blind Treatment Maintenance Phase | Removed text from footnote requiring participants to record the exact date and time of on-site and at-home study intervention administration in their study intervention diary. | Recording time of study intervention administration in study intervention diary is required only for specific visits specified in the Schedule of Activities (see footnotes). Only recording of date is required for all study intervention administrations. |
| 1.3.1 Schedule of Activities During the Screening and Open-Label Treatment Phases | 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. |
| 5.2 Exclusion Criteria | Added “DSM-5” to exclusion criterion 23 and added a note identifying the DSM-5 sexual dysfunction definition. | Added to specify the criteria to be used for diagnosis of these respective disorders. |
| 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. |

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| 8. Study Assessments and Procedures | Added "if applicable" to the text "remote contact visits (ie, telemedicine visits, conducted via phone or video conference". | Clarified that remote contact visits by video conference may not be applicable. |
| | Removed the following two materials from the list of study-specific materials:<br>• MGH ATRQ guidance document<br>• Rater qualifications/requirements for select clinician-administered assessments | The two study-specific materials will not be provided. |
| | Added "(where permitted)" to the text "Engage: A Smartphone Application used for video and audio teleconferencing". | Clarified audio recording is flexible. |
| | Removed "video" from text describing audio/video being captured on the vendor's conduit server and added the following text "audio recording (if applicable)". | No video recordings will be collected and audio recording may be collected. |
| 8.2.1 Montgomery-Åsberg Depression Rating Scale (MADRS) | Changed language from "All MADRS assessments will be audio recorded" to "MADRS assessments may be audio recorded". | Audio recording of MADRS assessments is not mandatory. |
| 9.3.3 Key Secondary 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.<br><br>Clarified that a sandwich variance estimator will be used if a structured covariance matrix is implemented.<br><br>Provided justification of unconditional multiple reference multiple imputation for missing data. | 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 and edited language 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. |
| 10.2.12 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 "This list of medications is not all-inclusive. For example, not all antibiotics within the listed classes may be excluded; specific cases may be discussed with the Medical Monitor, prior initiating a medication listed below." | Additional language allows for flexibility in assessments of medications when used in the study. |
| | Added "for continuous use" and "New benzodiazepine restriction not applicable for episodic use" to the benzodiazepines row of the prohibited medications table. | Additional language clarified when benzodiazepines were intended to be taken. |

| Section number and Name | Description of Change | Brief Rationale |
|---|---|---|
| | Removed “by 7 days before” from “participant must be on monotherapy by 7 days before first dose of study intervention)” and updated language. | Participants are not required to by on monotherapy by 7 days before first dose of study intervention. |
| Throughout the protocol | Minor grammatical, formatting, or spelling changes were made. | Minor errors were noted and corrected. |

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## LIST OF IN-TEXT FIGURES

### FIGURES

## ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ABV | alcohol-by-volume |
| 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] |
| CCI | [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 |
| EMP | end-of-maintenance phase |
| EOP-I | end-of-phase, open-label initial treatment phase |
| EOP-S | end-of-phase, open-label treatment stabilization phase |
| CCI [redacted] | [redacted] |
| EU | European Union |
| EW | early withdrawal |
| FAS | Full Analysis Set |
| FAS_SF | Full Analysis Set-Sexual Function |
| FDA | Food and Drug Administration |
| FOIA | Freedom of Information Act |
| FSH | follicle stimulating hormone |
| $FT_4$ | free thyroxine |
| CCI | [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 |
| $IC_{50}$ | maximal inhibition |
| ICE | intercurrent event |
| ICF | informed consent form |

| | |
|---|---|
| ICH | International Council for Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IEC | Independent Ethics Committee |
| INR | international normalized ratio |
| IP | investigational product |
| IRB | Institutional Review Board |
| ITT | intent-to-treat |
| IWRS | interactive web response system |
| JEISR | Janssen Electronic Inbound Safety Reporting |
| KR | kappa receptor |
| KRA | kappa receptor antagonist |
| LS | least-squares |
| LTM | Local Trial Managers |
| 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 |
| MR | mu receptor |
| NAcc | nucleus accumbens |
| 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) |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| CCI | [redacted] |
| QTc | corrected QT interval |
| QTcF | Corrected QT interval by 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 |
| WPAI:D | Work Productivity and Activity Impairment: Depression |

## Definitions of Terms

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

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

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

**IND:** 111006
**EU TRIAL NUMBER:** 2024-511057-22

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 patients 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 mu receptors (MRs) or delta receptors (DRs), may improve residual symptoms of depression, namely anhedonia, lassitude, and amotivation.

The present study will assess the efficacy of aticaprant 10 mg as an adjunctive therapy to current antidepressant treatment in delaying relapse of depressive symptoms in adult participants with MDD with moderate-to-severe anhedonia (MDD ANH+). This study will also assess the efficacy of continued adjunctive aticaprant treatment compared with adjunctive placebo in preventing the worsening of sexual function (SF).

**BENEFIT-RISK ASSESSMENT:**

While the safety, tolerability, and efficacy of aticaprant have been evaluated 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 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 as an adjunctive treatment for depressive symptoms, where the ultimate goal is to also effectively treat the remaining residual symptoms including anhedonia. To evaluate long-term maintenance of efficacy, the current study will assess a dosage of aticaprant 10 mg once daily, given as adjunctive therapy to an antidepressant, in delaying relapse of depressive symptoms in adult participants with MDD ANH+ who achieve a stable response after adjunctive OL treatment for 16 weeks.

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).

**OBJECTIVES AND ENDPOINTS**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To assess the efficacy of aticaprant 10 mg once daily compared with placebo once daily as adjunctive therapy to an antidepressant (SSRI/SNRI) in delaying relapse of depressive symptoms in the primary population (adult participants with MDD ANH+ who have achieved stable response). | • Time from randomization into the DB treatment maintenance phase to the first documentation of a relapse event |

| Objectives | Endpoints |
|---|---|
| **Key Secondary** | |
| To assess the efficacy of continued aticaprant 10 mg once daily compared with placebo once daily as adjunctive therapy to an antidepressant (SSRI/SNRI) in preventing the worsening of SF in the subpopulation of adult MDD ANH+ stable responder participants with sexual dysfunction (SDF) at OL baseline who have improvement in SF after OL treatment (16 weeks) with adjunctive aticaprant. | • Change in SF (measured by Changes in Sexual Functioning Questionnaire - short-form [CSFQ-14] total score) from DB baseline to end of Week 4 of the DB treatment maintenance phase |
| **Secondary** | |
| To assess the efficacy of aticaprant 10 mg once daily compared with placebo once daily as adjunctive therapy to an antidepressant (SSRI/SNRI) in the primary population (adult participants with MDD ANH+ who have achieved stable response) during DB treatment on the following: | |
| • Depressive symptoms (clinician- and patient-reported) | • Change from DB baseline to the end of DB treatment in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score<br>• Proportion of participants with remission of depressive symptoms over time, defined as a MADRS total score ≤10<br>• Proportion of participants with remission of depressive symptoms over time, defined as a Patient Health Questionnaire, 9-item (PHQ-9) total score ≤4<br>• Proportion of participants with response of depressive symptoms over time, defined as ≥50% improvement from OL baseline in the MADRS total score<br>• Proportion of participants with response of depressive symptoms over time, defined as ≥50% improvement from OL baseline in the PHQ-9 total score<br>• Change from DB baseline over time in the Clinical Global Impression - Severity (CGI-S) (depression) score<br>• Change from DB baseline over time in PHQ-9 total score |
| • Anhedonia symptoms (patient-reported) | • Change from DB baseline over time in anhedonia as assessed by the CCI [redacted] total score<br>• Change from DB baseline to the end of DB treatment in the Snaith-Hamilton Pleasure Scale (SHAPS)<br>• Proportion of participants who relapse and have evidence of anhedonia (defined as Item 1 [anhedonia-specific] PHQ-9 score of 2 or above) over time |
| • Anxiety symptoms (patient-reported) | • Change from DB baseline over time in the CCI [redacted] score |
| To assess the efficacy of aticaprant 10 mg once daily compared with placebo once daily as adjunctive therapy to an antidepressant (SSRI/SNRI) during the DB treatment maintenance phase in the primary population (adult participants with MDD ANH+ who have achieved stable response) with evidence of SDF at OL baseline and improvement in SF at the end of OL treatment stabilization phase. | |
| • SF (patient-reported) | • Change from DB baseline over time in SF (measured by CSFQ-14 total score) and SF domain scores (desire/interest; desire/frequency; completion/orgasm of CSFQ-14) |
| **Safety** | |
| Safety will be assessed in all participants. | |
| To assess the safety and tolerability of aticaprant 10 mg once daily (all treatment phases) compared with placebo once daily (DB treatment maintenance phase) as adjunctive therapy to an antidepressant in participants with MDD ANH+ | • AEs including AEs of special interest (AESIs)<br>• Vital signs including weight, body mass index (BMI)<br>• Suicidality assessment using the Columbia Suicidality Severity Rating Scale (C-SSRS)<br>• Laboratory values and ECGs |

**Hypothesis:**

The hypothesis of the study is that adjunctive aticaprant is superior to adjunctive placebo in delaying relapse of depressive symptoms in participants with MDD ANH+ who have had an inadequate response to treatment with an SSRI/SNRI and subsequently achieved stable response after OL treatment with adjunctive aticaprant.

**OVERALL DESIGN:**

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

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 OL 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 including the current SSRI/SNRI, 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 depressive episode. An inadequate response is defined as <50% reduction in depressive symptom severity as assessed by the MGH ATRQ, but with some improvement (>0%). Additionally, participants must have moderate-to-severe depression with MADRS total score ≥25 during screening and OL baseline without a clinically significant improvement (ie, an improvement of more than 20% on their MADRS total score) between the screening and the OL baseline assessments. A Site Independent Qualification Assessment (SIQA) will also assess the validity of the participants' current MDE, symptom severity, and antidepressant treatment response for inclusion in the study.

The study will consist of the following phases: Screening phase (up to 30 days prior to first dose administration), OL initial treatment phase (6 weeks), OL treatment stabilization phase (10 weeks), DB treatment maintenance phase (variable duration), follow-up phase (up to 2 weeks).

During the entire study, all participants will continue their current SSRI/SNRI antidepressant (one only) at the same dose without change.

All participants in the OL initial treatment phase (6 weeks) will receive adjunctive aticaprant 10 mg once daily.

Participants who respond (defined as ≥50% reduction in the MADRS total score from the OL baseline to the end of the OL initial treatment phase [Week 6]) to adjunctive aticaprant (10 mg once daily) may be eligible to proceed to the OL treatment stabilization phase.

In the OL treatment stabilization phase, the initial responders (after 6 weeks of treatment) will continue to receive OL adjunctive aticaprant (10 mg once daily) for another 10 weeks to confirm the stable improvement in depressive symptoms.

Participants who are stable responders (criteria will be blinded to sites) after a total of 16 weeks of treatment in the OL treatment phases will be randomly assigned in a 1:1 ratio to receive adjunctive aticaprant 10 mg once daily or adjunctive placebo once daily during the DB maintenance phase. Participants who do not

meet the blinded criteria for stable response at the end of the OL treatment stabilization phase will also proceed into the DB treatment maintenance phase using a sham randomization and will continue to receive adjunctive aticaprant 10 mg once daily.

Participants will continue in the DB treatment maintenance phase until they have a confirmed relapse or the sponsor terminates the study once the required number of relapses have been achieved. Depression relapse is defined as any of the following:

- MADRS total score ≥22 for 2 consecutive assessments separated by 7 days
- Hospitalization or observation for worsening of depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness, such as active suicidal ideation with intent or evidence of suicidal behavior based on the C-SSRS, suicide attempt, completed suicide, or hospitalization for suicide prevention.

For other questionable cases, a blinded Independent Relapse Adjudication Committee will determine if an event is a relapse event.

If the relapse is not confirmed, participants will resume the regular visit schedule.

Participants who have not relapsed and discontinue study intervention during the DB treatment maintenance phase for reasons other than withdrawal of consent will be encouraged to continue with additional follow-up visits after the EW visit until they relapse or the study is terminated by the sponsor. The same criteria for relapse as described for the DB treatment maintenance phase will be applied to identify a relapse during the follow-up phase; questionable cases will be evaluated by the Independent Relapse Adjudication Committee.

A participant will be considered to have completed the study if the participant completed the DB treatment maintenance phase (ie, had a relapse or was relapse-free in the DB treatment maintenance phase when the study is terminated).

Participants who discontinue study intervention for any reason other than a relapse or study termination in the DB treatment maintenance phase will not be considered to have completed the study. Any participant who prematurely discontinues study intervention during the OL treatment phases, is a non-responder at the end of initial OL treatment, or is ongoing in the OL treatment phases when the study is terminated will not be considered to have completed the study.

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) and an Independent Relapse Adjudication Committee will be commissioned for this study.

**NUMBER OF PARTICIPANTS:**

Approximately 660 participants will be enrolled in the OL initial treatment phase to achieve a target of 330 participants who have a stable response at the end of the OL treatment stabilization phase (ie, stable responders) and enter the DB treatment maintenance phase.

**STUDY ARMS AND DURATION:**

A summary of the study arms, study intervention, dosage level, and route of administration are presented below.

**Description of Interventions**

| | OL Initial Treatment Phase, OL Treatment Stabilization Phase, and DB Treatment Maintenance Phase: Group/Arm A | DB Treatment Maintenance Phase: Group/Arm B |
|---|---|---|
| **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 will be variable, depending on whether the participant meets phase-specific criteria (ie, criteria for response at the end of the OL initial treatment phase or relapse during the DB treatment maintenance phase) and the time that the study is terminated (ie, number of required relapse events achieved).

**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 PHQ-9, CSFQ-14, CCI [redacted] and Work Productivity and Activity Impairment: depression questionnaire (WPAI:D).

**PHARMACOKINETIC EVALUATIONS:**

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

**BIOMARKER EVALUATIONS:**

Blood samples will be collected: (a) to explore effect of biomarker signature status on maintenance of effect/relapse propensity; (b) to explore biomarkers that help to explain interindividual variability in efficacy, safety, and tolerability of adjunctive aticaprant, or that may be associated with MDD in general and/or specific symptoms, such as anhedonia.

**SAFETY EVALUATIONS:**

Safety evaluations will include collection of AEs and concomitant medications, physical examinations including a brief neurologic examination, body weight, BMI, vital signs, 12-lead ECG, urine drug test, alcohol breath test, clinical laboratory tests, pregnancy tests, menstrual cycle tracking, and C-SSRS.

**STATISTICAL METHODS**

**Sample Size Calculation:**

The maximum number of events required for the study is approximately 127, which provides 90% power to detect a hazard ratio of 0.562 at the 1-sided significance level of 0.025 (equivalent to 2-sided 0.05), to detect superiority of aticaprant compared with placebo (both as an adjunctive treatment) in delaying relapse of depressive symptoms in adult participants with MDD ANH+ who are stable responders.

A total of approximately 330 participants with stable response will need to be randomized (in a 1:1 ratio to either continue with adjunctive aticaprant 10 mg or receive adjunctive placebo after discontinuation of adjunctive aticaprant) to obtain approximately 127 relapse events based on an accrual period of 24 months, DB treatment maintenance phase duration of 26 months, and a 6-month drop-out rate of 25%.

Assuming a stable response rate of 50%, approximately 660 participants are to be enrolled in the OL initial treatment phase of the study to obtain 330 stable responders for the DB treatment maintenance phase.

It is anticipated that of 330 participants randomized in the DB treatment maintenance phase, approximately 182 participants will be evaluable for the assessment of SF. If the hypothesis for the primary endpoint is

rejected, the study is powered at 80% to detect an effect size of 0.44 for the change in CSFQ-14 total score at Week 4 in the DB treatment maintenance phase.

**Efficacy Analyses:**

Primary Efficacy Endpoint:

The primary endpoint is the time from randomization into the DB treatment maintenance phase to the first documentation of a relapse event in participants with MDD ANH+ who achieve a stable response at the end of the OL treatment stabilization phase. The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method. The primary analysis of study intervention differences will be conducted using an unstratified log-rank test.

Key Secondary Endpoint:

The key secondary endpoint is the change in SF (measured by CSFQ-14) from DB baseline to end of Week 4 of the DB treatment maintenance phase in MDD ANH+ stable responder participants with SDF at OL baseline who have improvement in SF after OL treatment (16 weeks) with adjunctive aticaprant. Change from the DB baseline to Week 4 of the DB treatment maintenance phase in CSFQ-14 total score will be analyzed by a Mixed-effect Model for Repeated Measures (MMRM).

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 a 2-sided 0.05 level accounting for multiplicity due to the primary (time to relapse of depression) and the key secondary (change in CSFQ-14 total score) efficacy endpoints.

Secondary Efficacy Endpoints:

For stable responders, treatment comparison between adjunctive aticaprant and adjunctive placebo in the change from DB baseline to endpoint in MADRS total score and CCI total score during the DB treatment maintenance phase will be performed using an analysis of covariance model with country/territory and study intervention as factors and DB baseline value as a covariate.

**Safety Analyses:**

Safety data including but not limited to AEs, SAEs, AESIs (CCI CCI laboratory assessments, ECG measurements, and vital signs will be summarized by study intervention group.

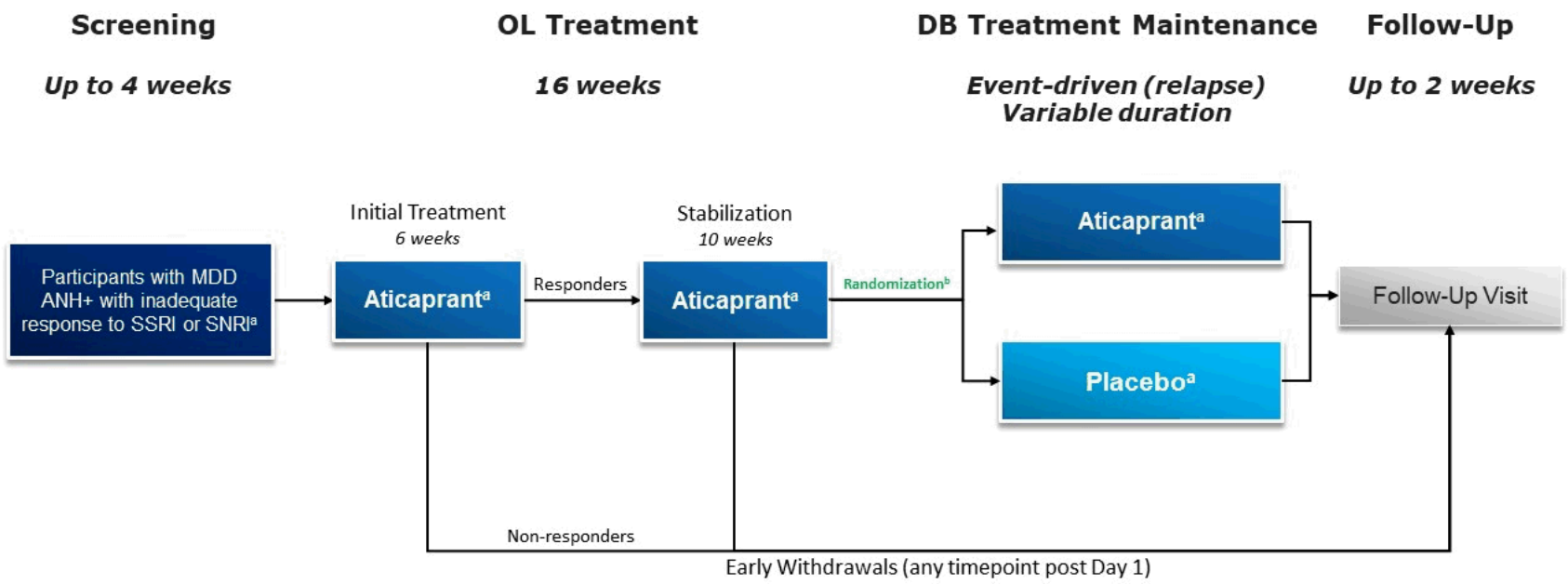
Suicide-related thoughts and behaviors based on the C-SSRS will be tabulated by study intervention group.

**Interim Analysis:**

To evaluate the assumptions used in the sample size calculation, relapse rates will be monitored sequentially during the DB treatment maintenance phase. The IA will be performed after approximately a total of 60 relapse events (of the 127 maximum) are observed in stable responders. The intent of the IA is to perform event re-estimation. Adjustments made to the required number of events will not be revealed to the study team. Treatment difference will be compared using a log-rank test. A futility analysis may be conducted at the IA. An IDMC will review the IA results.

## 1.2. Schema

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




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

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

## 1.3. Schedule of Activities (SoA)

### 1.3.1. Schedule of Activities During the Screening and Open-Label Treatment Phases

| Phase | Screening[a] | | OL Initial Treatment | | | | | OL Treatment Stabilization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | OL Baseline | | | | EOP-I[d] | | | | | EOP-S[d,e] |
| Visit Number | 1.1 | 1.2[b,c] | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | 3.1 | 3.2 | 3.3 | 3.4 | 3.5 |
| Study Day | -30 to -2 | | 1 | 8 | 15 | 29 | 43 | 57 | 71 | 85 | 99 | 113 |
| Study Week | | | | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
| Clinic Visit (C) or Remote Contact (RC) | C | C or RC | C | RC | C | C | C | C | RC | C | RC | C |
| Visit window (days) | | | | ±2 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 |
| **Study Procedure** | | | | | | | | | | | | |
| **Screening/Administrative** | | | | | | | | | | | | |
| Informed consent (ICF)[f] | X | | | | | | | | | | | |
| ICF for optional real-world data collection substudy (US only) | X | | | | | | | | | | | |
| Medical history, psychiatric history, SF history, demographics | X | | | | | | | | | | | |
| Employment status | X | | | | | | X | | | | | X |
| Inclusion/exclusion criteria[g] | X | | X | | | | | | | | | |
| SCID-CT | X | | | | | | | | | | | |
| MGH ATRQ | X | | | | | | | | | | | |
| SIQA | X[h] | | | | | | | | | | | |
| Prestudy therapy | X | | | | | | | | | | | |
| Preplanned surgery/procedure(s) | X | | | | | | | | | | | |
| Diary for current antidepressant compliance (Dispense/Review) | X | | X | | X | | X | | | X | | X |
| Evaluation of current antidepressant compliance[i] | X | | X | | | | X | | | | | X |

| Phase | Screening[a] | | OL Initial Treatment | | | | | OL Treatment Stabilization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | OL Baseline | | | | EOP-I[d] | | | | | EOP-S[d,e] |
| Visit Number | 1.1 | 1.2[b,c] | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | 3.1 | 3.2 | 3.3 | 3.4 | 3.5 |
| Study Day | -30 to -2 | | 1 | 8 | 15 | 29 | 43 | 57 | 71 | 85 | 99 | 113 |
| Study Week | | | | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
| Clinic Visit (C) or Remote Contact (RC) | **C** | **C or RC** | **C** | **RC** | **C** | **C** | **C** | **C** | **RC** | **C** | **RC** | **C** |
| Visit window (days) | | | | ±2 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 |
| **Study Procedure** | | | | | | | | | | | | |
| Serum pregnancy test[j] | X | | | | | | | | | | | |
| Urine pregnancy test[j] | | | X | | | | X | | | X | | X |
| Height | X | | | | | | | | | | | |
| Weight | X | | | | | | X | | | | | X |
| **Study Intervention Administration** | | | | | | | | | | | | |
| Dispense study intervention | | | X | | X | X | X[k] | X | | X | | X[l] |
| Dispense/review study intervention diary[m] | | | X | | X | X | X[k] | X | | X | | X[l] |
| Return/Drug Accountability | | | | | X | X | X | X | | X | | X |
| Study intervention administration[n] | | | ← Continuous → | | | | | | | | | |
| **Efficacy Assessments[o]** | | | | | | | | | | | | |
| MADRS (Site Rater, SIGMA version)[p] | X | | X | | X | X | X | X | X | X | X | X |
| CGI-S (depression) | | | X | | X | X | X | X | X | X | X | X |
| SHAPS | X | | X | | | | X | | | | | X |
| CCI [redacted] | | | X | | | | X | | | X | | X |
| PHQ-9 | | | X | | | | X | | | X | | X |
| CSFQ-14 | | | X | | X | X | X | X | | X | | X |
| CCI [redacted] | | | X | | X | X | X | X | | X | | X |
| CCI [redacted] | | | X | | | | X | | | | | X |
| CCI [redacted] | | | X | | | | X | | | | | X |
| CCI [redacted] | | | X | | | | X | | | | | X |

| Phase | Screening[a] | | OL Initial Treatment | | | | | OL Treatment Stabilization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | OL Baseline | | | | EOP-I[d] | | | | | EOP-S[d,e] |
| Visit Number | 1.1 | 1.2[b,c] | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | 3.1 | 3.2 | 3.3 | 3.4 | 3.5 |
| Study Day | -30 to -2 | | 1 | 8 | 15 | 29 | 43 | 57 | 71 | 85 | 99 | 113 |
| Study Week | | | | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
| Clinic Visit (**C**) or Remote Contact (**RC**) | **C** | **C or RC** | **C** | **RC** | **C** | **C** | **C** | **C** | **RC** | **C** | **RC** | **C** |
| Visit window (days) | | | | ±2 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 |
| **Study Procedure** | | | | | | | | | | | | |
| WPAI:D | | | X | | | | X | | | | | X |
| **Safety Assessments** | | | | | | | | | | | | |
| Physical examination | X | | X | | | | X | | | | | X |
| 12-lead ECG | X | | X | | | | X[q] | | | | | X[q] |
| Vital signs | X | | X | | | | X | | | | | X |
| Urine drug test | X | | X | | | | X | | | | | X |
| Alcohol breath test | X | | X | | | | X | | | | | X |
| C-SSRS: Screening/Baseline (Lifetime) version | X | | | | | | | | | | | |
| C-SSRS: Since last visit version | | X | X | X | X | X | X | X | X | X | X | X |
| Menstrual cycle tracking (start date of last menstrual period prior to study visit)[r] | X | | X | | | | X | | | X | | X |
| **Clinical Laboratory Tests** | | | | | | | | | | | | |
| Hematology, chemistry | X | | X | | | | X | | | | | X |
| Lipid panel (fasting) | X | | | | | | | | | | | |
| Urinalysis | X | | | | | | X | | | | | X |
| TSH/$FT_4$; HbA1c | X | | | | | | | | | | | |
| **Clinical Pharmacology Assessments** | | | | | | | | | | | | |
| PK blood sample collection[n] | | | | | | | | | | | | X |

| Phase | Screening[a] | | OL Initial Treatment | | | | | OL Treatment Stabilization | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | OL Baseline | | | | EOP-I[d] | | | | | EOP-S[d,e] |
| Visit Number | 1.1 | 1.2[b,c] | 2.1 | 2.2 | 2.3 | 2.4 | 2.5 | 3.1 | 3.2 | 3.3 | 3.4 | 3.5 |
| Study Day | -30 to -2 | | 1 | 8 | 15 | 29 | 43 | 57 | 71 | 85 | 99 | 113 |
| Study Week | | | | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
| Clinic Visit (**C**) or Remote Contact (**RC**) | **C** | **C or RC** | **C** | **RC** | **C** | **C** | **C** | **C** | **RC** | **C** | **RC** | **C** |
| Visit window (days) | | | | ±2 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 |
| **Study Procedure** | | | | | | | | | | | | |
| **Biomarkers Assessments** | | | | | | | | | | | | |
| Morning blood sample collection (fasting)[s] | | | X | | | | | | | | | X |
| **Ongoing Review** | | | | | | | | | | | | |
| Concomitant therapy | ← Continuous → | | | | | | | | | | | |
| Adverse events | ← Continuous → | | | | | | | | | | | |

**Abbreviations:** see ABBREVIATIONS AND DEFINITIONS OF TERMS.

**Notes:**

At OL baseline (Visit 2.1, Day 1), MADRS, PROs, CGI-S, and C-SSRS must be completed prior to dosing. It is recommended that procedures should be performed in the following sequence: interview with qualified site-based rater (MADRS [SIGMA version], if not completed via videoconference before the actual visit) to confirm eligibility, blood samples and urine collection, breakfast, 12-lead ECGs, vital signs, PROs, CGI-S, C-SSRS, other safety assessments, followed by dosing. At the EOP-S visit (Visit 3.5) with fasting blood sampling for biomarker assessments, it is recommended that procedures should be performed in the following sequence: 12-lead ECGs, vital signs, blood samples and urine collection, dosing, breakfast, PROs, interview with qualified site-based rater (MADRS [SIGMA version], if not completed via videoconference before the actual visit; CGI-S), C-SSRS, and other safety assessments.

**Footnotes:**

a. All screening assessments performed at Visits 1.1 and 1.2 may be split across different days provided that all screening assessments are performed early enough in order to obtain the results and confirm the eligibility prior to OL baseline (Visit 2.1). Retesting of abnormal laboratory value(s) that may lead to exclusion will be allowed once during the screening phase.

b. If needed, the screening phase may be extended for up to 3 additional weeks to allow for tapering and discontinuation of any ongoing prohibited therapies before OL baseline. Tapering or time of discontinuation of prohibited therapies should be based on potential drug-drug interactions, local prescribing information, or clinical judgment 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 tapered discontinuation of their prohibited treatment(s) can immediately proceed to the OL initial treatment phase and have their OL baseline (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 OL initial treatment phase or OL treatment stabilization phase for reasons other than withdrawal of consent, an EW visit (refer to Schedule of Activities for Early Withdrawal Visit and Follow-up Phase) should be conducted followed by the follow-up phase; Visit 5.1 in the follow-up phase is their final study visit. If the EW visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
**Note:** Participants in either OL phase who have not yet completed the phase when the study is terminated will be given the opportunity to complete their current phase, have an EW visit conducted at Week 6 or Week 16, as applicable, and then enter the follow-up phase; Visit 5.1 in the follow-up phase is their final study visit.
e. Visit 3.5 (Week 16) of the OL treatment stabilization phase and Visit 4.1 (Week 16) of the DB treatment maintenance phase are performed on the same day. Results for all assessments performed at Visit 3.5 will also serve as baseline for the DB treatment maintenance phase and must be completed before randomization (Visit 4.1 [see SoA for DB treatment maintenance phase]).
f. 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.
g. Verify inclusion/exclusion criteria before enrollment of each participant.
h. The SIQA interview will include an additional MADRS assessment performed remotely by independent raters to confirm the site's evaluation of depression severity. The remote interview will be scheduled as soon as possible after Visit 1.1 and is to occur within the first 2 weeks of the screening phase.
i. During the screening phase, compliance to the current SSRI/SNRI treatment must be confirmed by documented records (eg, medical/pharmacy/prescription record, a letter from a treating physician). During the OL initial treatment phase and OL treatment stabilization phase, compliance to the current SSRI or SNRI 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.
j. Applicable to female participants of childbearing potential.
k. Study intervention and the study intervention diary are dispensed for participants who have a response (ie, ≥50% reduction in the MADRS total score from the OL baseline at Week 6) and continue into the OL treatment stabilization phase.
l. Study intervention and the study intervention diary are dispensed for participants who continue into the DB treatment maintenance phase (ie, after randomization at Visit 4.1 [see SoA for DB treatment maintenance phase]).
m. Dispense the study intervention diary at Visit 2.1 and review it at subsequent clinic visits (C) indicated in SoA.
n. 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. On days with PK blood sample collection, participants will be asked not to take study intervention in the morning before they come to the site as the study intervention will be self-administered on-site from the blisters dispensed at that visit and witnessed by the investigator or a properly trained designee. The study intervention should be administered after PK blood sample collection and other specified procedures are completed. 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 blood sample collection.
o. All PRO assessments should be conducted in the order listed in the above SoA table. Except at visits described in the Notes above (OL Baseline and EOP-S), PROs should be completed first prior to other assessments.
p. To reduce the time spent by a participant on-site during clinic visits, it is recommended for sites to consider scheduling and conducting the MADRS assessment (with videoconferencing) before or after the on-site visit but respecting the visit window.
**Note:** At the EOP-S visit (Visit 3.5), the MADRS must be performed **before (**respecting the -3 day visit window) **or at the on-site visit**.
q. If a clinically significant finding is identified in QTcF, the average QTcF of three 12-lead ECGs, recorded 4 minutes apart, will be used to assess QTc stopping criteria.
r. Only applicable to female participants with a menstrual cycle.
s. Biomarker sample will be collected prior to study intervention administration.

### 1.3.2. Schedule of Activities During the Double-blind Treatment Maintenance Phase

| Phase | DB Treatment Maintenance | | | | |
|---|---|---|---|---|---|
| | DB Baseline[a] | Every 2 weeks | Every 4 weeks | Unscheduled for relapse confirmation[b] | EMP[b,c] |
| Visit Number | 4.1 | | | | 4.X |
| Study Day | 113 | | | | |
| Study Week | 16 | | | | |
| Clinic Visit (C) or Remote Contact (RC) | **C** | **DB Week 2: C<br>All others: RC** | **C** | **C or RC** | **C** |
| Visit window (days) | ±3 | ±3 | ±3 | | +7 |
| **Study Procedure** | | | | | |
| **Screening/Administrative** | | | | | |
| Employment status | | | | | X |
| Diary for current antidepressant compliance (Dispense/Review) | | | X | | X |
| Evaluation of current antidepressant compliance[d] | | | X | | X |
| Urine pregnancy test[e] | | | X | | X |
| Weight | | | | | X |
| **Study Intervention Administration** | | | | | |
| Randomization | X | | | | |
| Dispense study intervention | X | | X | | |
| Dispense/review study intervention diary[f] | X | | X | | X |
| Return/Drug Accountability | | | X | | X |
| Study intervention administration[g] | ← | ——— | Continuous | ——— | → |
| **Efficacy Assessments[h]** | | | | | |
| MADRS (Site Rater, SIGMA version)[b,i] | | X | X | X[j] | X[j] |
| CGI-S (depression) | | X | X | | X |
| SHAPS | | | X | | X |
| CCI | | | X | | X |
| PHQ-9 | | | X | | X |
| CSFQ-14 | | **X (only at DB Week 2)** | X | | X |
| CCI | | | X | | X |
| CCI | | | X | | X |
| CCI | | | X | | X |
| CCI | | | X | | X |
| WPAI:D | | | X | | X |

| Phase | DB Treatment Maintenance | | | | |
|---|---|---|---|---|---|
| | DB Baseline[a] | Every 2 weeks | Every 4 weeks | Unscheduled for relapse confirmation[b] | EMP[b,c] |
| Visit Number | 4.1 | | | | 4.X |
| Study Day | 113 | | | | |
| Study Week | 16 | | | | |
| Clinic Visit (**C**) or Remote Contact (**RC**) | **C** | **DB Week 2: C<br>All others: RC** | **C** | **C or RC** | **C** |
| Visit window (days) | ±3 | ±3 | ±3 | | +7 |
| **Study Procedure** | | | | | |
| **Safety Assessments** | | | | | |
| Physical examination | | | X | | X |
| 12-lead ECG[k] | | | X (every 12 weeks) | | X |
| Vital signs | | | X | | X |
| Urine drug test | | | X | | X |
| Alcohol breath test | | | X (every 12 weeks) | | |
| C-SSRS: Since last visit version | | X | X | | X |
| Menstrual cycle tracking (start date of last menstrual period prior to study visit)[l] | | | X | | X |
| **Clinical Laboratory Tests** | | | | | |
| Hematology, chemistry | | | X (every 12 weeks) | | X |
| Urinalysis | | | X (every 12 weeks) | | X |
| **Clinical Pharmacology Assessments** | | | | | |
| PK blood sample collection[g] | | | X (Week 4 only) | | |
| **Biomarkers Assessments** | | | | | |
| Morning blood sample collection (fasting)[m] | | | | | X |
| **Ongoing Review** | | | | | |
| Concomitant therapy | ← | | Continuous | | → |
| Adverse events | ← | | Continuous | | → |

**Abbreviations:** see ABBREVIATIONS AND DEFINITIONS OF TERMS.

**Note:**

During the EMP visit with fasting blood sampling for biomarker assessments, it is recommended that procedures should be performed in the following sequence: 12-lead ECGs, vital signs, blood samples and urine collection, dosing, breakfast, PROs, interview with qualified site-based rater (MADRS [SIGMA version], if not completed via videoconference before the actual visit; CGI-S), C-SSRS, and other safety assessments.

**Footnotes:**

a. Visit 3.5 (Week 16) of the OL treatment stabilization phase and Visit 4.1 (Week 16) are performed on the same day. Results for all assessments performed at Visit 3.5 will also serve as baseline for the DB treatment maintenance phase and must be completed before randomization.

b. Participants who have a MADRS total score ≥22 at any time point during the DB treatment maintenance phase, will have an unscheduled consecutive MADRS assessment conducted separated by 7 (±3) days to confirm the relapse. If the MADRS assessment is performed remotely and relapse is confirmed, participants will return to the site to perform an EMP visit within 7 days of relapse confirmation. If the unscheduled MADRS assessment for relapse confirmation is performed on-site, the EMP visit will be performed on the same day and duplicate assessments are not required. If the relapse is not confirmed, participants will resume the regular visit schedule.

c. If a participant prematurely discontinues the study intervention before the end of the DB treatment maintenance phase for reasons other than withdrawal of consent, an EW visit (refer to Schedule of Activities for Early Withdrawal Visit and Follow-up Phase) should be conducted, followed by the follow-up phase. If the EW visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.
**Note:** participants who have not yet completed the DB Week 4 visit in this phase when the study is terminated, will be encouraged to continue study intervention through DB Week 4 or at least complete assessments through the DB Week 4 visit. At DB Week 4, these participants will have an EMP visit conducted and then enter the follow-up phase.

d. During the DB treatment maintenance phase, compliance to the current SSRI or SNRI 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.

e. Applicable to female participants of childbearing potential.

f. Dispense the study intervention diary at Visit 4.1 and review it at subsequent clinic visits (C) indicated in SoA.

g. The first administration of randomized study intervention on Day 113 (Visit 4.1) will occur on-site. At home: study intervention should be taken around the same time and preferably in the morning. On days with PK blood sample collection, participants will be asked not to take study intervention in the morning before they come to the site as the study intervention will be self-administered on-site from the blisters dispensed at that visit and witnessed by the investigator or a properly trained designee. The study intervention should be administered after PK blood sample collection and other specified procedures are completed. 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 blood sample collection.

h. All PRO assessments should be conducted in the order listed in the above SoA table. Except at the EMP visit described in the Note above, PROs should be completed first prior to other assessments.

i. To reduce the time spent by a participant on-site during clinic visits, it is recommended for sites to consider scheduling and conducting the MADRS assessment (with videoconferencing) before or after the on-site visit but respecting the visit window.

j. If the MADRS confirming the relapse is performed within 7 days before the EMP visit, the assessment does not need to be repeated at the EMP visit.

k. If a clinically significant finding is identified in QTcF, the average QTcF of three 12-lead ECGs, recorded 4 minutes apart, will be used to assess QTc stopping criteria.

l. Only applicable to female participants with a menstrual cycle.

m. Biomarker sample will be collected prior to study intervention administration.

### 1.3.3. Schedule of Activities for Early Withdrawal Visit and Follow-up Phase

| Phase | Early Withdrawal Visit | Follow-up Phase | Additional Follow-up for Early Withdrawal of Study Intervention During DB Treatment Maintenance Phase (Non-relapsers Only) | Additional Follow-up Unscheduled for relapse confirmation[c] |
|---|---|---|---|---|
| Visit Number | EW[a] | 5.1[b] | Additional FU | |
| Clinic Visit (C) or Remote Contact (RC) | C | C | C | C or RC |
| Visit window (days) | +7 | 14 ±7 days after EMP or EW | Every 8 weeks (+4 weeks) after Visit 5.1 (follow-up visit) | |
| **Study Procedure** | | | | |
| **Administrative** | | | | |
| Employment status | X | | | |
| Diary for current antidepressant compliance (Review) | X | | | |
| Evaluation of current antidepressant compliance[d] | X | | | |
| Urine pregnancy test[e] | X | | | |
| Weight | X | | | |
| **Study Intervention Administration** | | | | |
| Review study intervention diary | X | | | |
| Return/Drug Accountability | X | | | |
| **Efficacy Assessments[f]** | | | | |
| MADRS (Site Rater, SIGMA version)[g] | X | X | X | X |
| CGI-S (depression) | X | X | X | |
| SHAPS | X | | | |
| CCI | X | X | X | |
| PHQ-9 | X | X | X | |
| CSFQ-14 | X | X | X | |
| CCI | X | | | |
| CCI | X | | | |
| CCI | X | | | |
| CCI | X | | | |
| WPAI:D | X | | | |
| **Safety Assessments** | | | | |
| Physical examination | X | | | |
| 12-lead ECG | X | | | |
| Vital signs | X | | X | |

| Phase | Early Withdrawal Visit | Follow-up Phase | Additional Follow-up for Early Withdrawal of Study Intervention During DB Treatment Maintenance Phase (Non-relapsers Only) | Additional Follow-up Unscheduled for relapse confirmation[c] |
|---|---|---|---|---|
| Visit Number | EW[a] | 5.1[b] | Additional FU | |
| Clinic Visit (C) or Remote Contact (RC) | C | C | C | C or RC |
| Visit window (days) | +7 | 14 ±7 days after EMP or EW | Every 8 weeks (+4 weeks) after Visit 5.1 (follow-up visit) | |
| **Study Procedure** | | | | |
| Urine drug test | X | | | |
| C-SSRS: Since last visit version | X | X | X | |
| Menstrual cycle tracking (start date of last menstrual period prior to study visit)[h] | X | | | |
| **Clinical Laboratory Tests** | | | | |
| Hematology, chemistry | X | | | |
| Urinalysis | X | | | |
| **Clinical Pharmacology Assessments** | | | | |
| PK blood sample collection[i] | X | | | |
| **Biomarkers Assessments** | | | | |
| Morning blood sample collection (fasting) | X | | | |
| **Ongoing Review** | | | | |
| Concomitant therapy | ← Continuous → | | | |
| Adverse events | ← Continuous → | | | |

**Abbreviations:** see ABBREVIATIONS AND DEFINITIONS OF TERMS.

**Note:**

During the EW visit with fasting blood sampling for biomarker assessments, it is recommended that procedures should be performed in the following sequence: 12-lead ECGs, vital signs, blood samples and urine collection, breakfast, PROs, interview with qualified site-based rater (MADRS [SIGMA version], if not completed via videoconference before the actual visit; CGI-S), C-SSRS, and other safety assessments.

**Footnotes:**

a. If EW visit is conducted on the same day as a scheduled visit, duplicate assessments are not required.

b. Follow-up Visit 5.1 is the final study visit for participants who discontinue study intervention before the end of the OL initial treatment, OL treatment stabilization, or who have completed the OL initial treatment phase but are not eligible to continue to the OL treatment stabilization phase and for those participants who relapse during the DB treatment maintenance phase.

c. Participants who have a MADRS total score ≥22 at any time point during the additional follow-up phase, will have an unscheduled consecutive MADRS assessment conducted separated by 7 (±3) days to confirm the relapse. If the relapse is not confirmed, participants will resume the regular visit schedule.
d. Compliance to the current SSRI or SNRI 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.
e. Applicable to female participants of childbearing potential.
f. All PRO assessments should be conducted in the order listed in the above SoA table. Except at the EW visit described in the Note above, PROs should be completed first prior to other assessments.
g. To reduce the time spent by a participant on-site during clinic visits, it is recommended for sites to consider scheduling and conducting the MADRS assessment (with videoconferencing) before or after the on-site visit but respecting the visit window.
h. Only applicable to female participants with a menstrual cycle.
i. The exact date and time when the study intervention was last administered is required.

## 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; Lutz 2014; Marchette 2021; Rorick-Kehn 2014; Walker BM 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 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 studies and results from 2 well-controlled Phase 2 studies provide complimentary positive evidence for efficacy of aticaprant in patients with major depression with anhedonia. 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 their 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. CCI [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, Study Interventions Administered.

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 (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 ER 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 2006). In the seminal 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 2006). Poor response to first-line treatments for MDD such as SSRIs and SNRIs remains a significant problem resulting in persistent impairment and high utilization of health care resources (Kennedy N 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 antidepressant agents evaluated with respect to their effect on MDD and anhedonia have not shown pronounced collinear improvements in anhedonia symptoms (Cao 2019). As such there is an unmet need to identify new more targeted treatments addressing depression symptoms that are insufficiently managed by current antidepressants (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: MR, DR, and KR. The MR system is involved in analgesia, respiratory control, GI motility and is also believed to be involved in addiction. DRs 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 NAcc. The distribution of KRs in human brain has been described by in vivo positron emission tomography (PET) imaging with the selective KRA $^{11}$C-LY2795050 and dose-dependent occupancy has been demonstrated by aticaprant (Naganawa 2014, 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; Marchette 2021; Rorick-Kehn 2014; Walker BM 2008).

Functional effects of KR blockade by aticaprant on reward circuitry in human brain has been evaluated in a Phase 2a 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 consummatory subscale ($p<0.02$), although not on the anticipatory subscale (Krystal 2020; Pizzagalli 2020).

In 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**

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 SH 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, 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 SSRIs/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 present randomized, DB, placebo-controlled, parallel-group, multicenter study is being conducted to assess the efficacy of aticaprant 10 mg as an adjunctive therapy to current antidepressant treatment in delaying relapse of depressive symptoms in adult participants with MDD ANH+ who achieve a stable response after OL treatment with adjunctive aticaprant treatment for 16 weeks.

This study will also assess the efficacy of continued aticaprant treatment compared with placebo, each administered adjunctively with current antidepressant treatment, in preventing the worsening of SF in the subpopulation of adult MDD participants with SDF at study entry who have improvement in SF after 16 weeks of OL treatment with adjunctive aticaprant treatment.

## 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 processing, and may play a key role in mood, stress, and addictive disorders. Chronic stress, substance abuse, and acute substance withdrawal lead to increased dynorphin release, activating KRs, and subsequent downstream signaling pathways to inhibit phasic mesolimbic dopamine release, 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]

[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 [redacted]

***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 temporal experience of pleasure scale consummatory subscale ($p<0.02$). CCI [redacted]

CCI [redacted] (Krystal 2020; Pizzagalli 2020).

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 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 enriched ITT population (participants with <30% improvement during the placebo run-in period). In the full ITT population (all participants), 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 CCI [redacted] (8.2% vs 2.4%). TEAEs of special interest in the aticaprant group that were commonly reported were CCI [redacted] and CCI [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%), CCI (11.1% vs 2.3%), anxiety, insomnia, and suicidal ideation (each 6.7% vs 4.5%), CCI (6.8% vs 2.2%), and depression and rash (each 6.7% vs 0%).

CCI

## 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 and CCI 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.

Add-on oral placebo is being used as a double-blind control for add-on aticaprant to maintain study blinding in the DB treatment maintenance phase. All participants will continue to receive their current oral antidepressant throughout the study. Participants will not be on placebo alone. 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 compare aticaprant plus an oral antidepressant to placebo plus an oral antidepressant.

Participants will be closely monitored throughout the study with remote contacts with the study site every other week, regular on-site visits every 4 weeks, and unscheduled visits as needed. All participants will continue their current SSRI/SNRI antidepressant throughout the study for which they have had at least some symptom improvement previously. 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. As cases of relapse will constitute worsening of MDD symptoms which can be detected early, once relapse occurs, other interventions can be utilized to prevent further worsening of symptoms. These measures will help prevent any long-term consequences of the randomized withdrawal design.

### 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 10 mg added to an ongoing antidepressant, 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 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

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

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).

CCI [redacted]

[redacted]

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, Adverse Drug Reactions).

## 3. OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To assess the efficacy of aticaprant 10 mg once daily compared with placebo once daily as adjunctive therapy to an antidepressant (SSRI/SNRI) in delaying relapse of depressive symptoms in the primary population (adult participants with MDD ANH+ who have achieved stable response). | • Time from randomization into the DB treatment maintenance phase to the first documentation of a relapse event |
| **Key Secondary** | |
| To assess the efficacy of continued aticaprant 10 mg once daily compared with placebo once daily as adjunctive therapy to an antidepressant (SSRI/SNRI) in preventing the worsening of SF in the subpopulation of adult MDD ANH+ stable responder participants with SDF at OL baseline who have improvement in SF after OL treatment (16 weeks) with adjunctive aticaprant. | • Change in SF (measured by CSFQ-14 total score) from DB baseline to end of Week 4 of the DB treatment maintenance phase |

| Objectives | Endpoints |
|---|---|
| **Secondary** | |
| CCI [redacted] | |
| **Safety** | |
| Safety will be assessed in all participants. | |
| To assess the safety and tolerability of aticaprant 10 mg once daily (all treatment phases) compared with placebo once daily (DB treatment | • AEs including AESIs<br>• Vital signs including weight, BMI<br>• Suicidality assessment using the C-SSRS |

| Objectives | Endpoints |
|---|---|
| maintenance phase) as adjunctive therapy to an antidepressant in participants with MDD ANH+ | • Laboratory values and ECGs |
| **Exploratory** | |

CCI

[redacted]

**ESTIMANDS**

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

Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

**HYPOTHESIS**

The hypothesis of the study is that adjunctive aticaprant is superior to adjunctive placebo in delaying relapse of depressive symptoms in participants with MDD ANH+ who have had an inadequate response to treatment with an SSRI/SNRI and subsequently achieved stable response after OL treatment with adjunctive aticaprant.

# 4. STUDY DESIGN

## 4.1. Overall Design

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

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

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

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

Approximately 660 participants will be enrolled in the OL initial treatment phase to achieve a target of 330 participants who have a stable response at the end of the OL treatment stabilization phase (ie, stable responders) and enter the DB treatment maintenance phase. Participants who are stable responders will be randomly assigned in a 1:1 ratio to receive adjunctive aticaprant 10 mg once daily or adjunctive placebo once daily during the DB maintenance phase, while all participants continue their current SSRI/SNRI (one only) throughout the study. Additionally, since the MADRS criterion for stable response is blinded to the sites, participants who do not meet criteria for stable response at the end of the OL treatment stabilization phase will also proceed into the DB treatment maintenance phase using a sham randomization and will continue to receive aticaprant 10 mg orally once daily plus their current SSRI/SNRI.

An IDMC and an Independent Relapse Adjudication Committee will be commissioned for this study. Refer to Section 10.2.7 for details.

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

### 4.1.1. Study Interventions

Study intervention will be administered orally once daily preferably in the morning (with or without food). During the entire study, all participants will continue their current SSRI/SNRI

antidepressant (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.

All participants in the OL initial treatment phase (6 weeks) and participants who are eligible to continue into the OL treatment stabilization phase (10 weeks) will receive adjunctive aticaprant 10 mg once daily plus their current SSRI/SNRI. Participants who achieve stable response at the end of the OL stabilization phase and enter the DB treatment maintenance phase (variable length) will be randomly assigned to receive adjunctive aticaprant 10 mg once daily or adjunctive placebo once daily, while all participants continue their current SSRI/SNRI.

The maximum duration of participation will be variable, depending on whether the participant meets phase-specific criteria (ie, criteria for response at the end of the OL initial treatment phase or relapse during the DB treatment maintenance phase; see Section 4.1.7) and the time that the study is terminated (ie, number of required relapse events achieved).

### 4.1.2. Screening Phase

After providing signed informed consent, all the participants experiencing a 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 1.3.1).

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 CCI at screening and at OL baseline).

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 including the current SSRI/SNRI, administered at an adequate dose (at or above the minimum therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current depressive episode (see Section 5.1, Inclusion Criterion 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 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).

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 will also assess the validity of the participants' current MDE, symptom severity, and antidepressant treatment response for inclusion in the study.

All participants will continue their current antidepressant (SSRI/SNRI) therapy for the duration of the study. The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. Participants will be permitted to only continue one of these allowed antidepressants at an adequate and tolerated dose during the study. No changes in the current SSRI/SNRI antidepressant or dose are permitted from screening until the end of the DB treatment maintenance phase (see Section 6.9.1 for details). The sponsor will not supply these antidepressant medications.

Prohibited medications will be stopped prior to the start of the OL initial 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 OL initial treatment phase and can have their OL 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 until the last study visit.

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. Open-label Initial Treatment Phase

The OL initial treatment phase starts on the day of the first dose of aticaprant and continues for 6 weeks. Evaluations that will be performed at each visit during this phase are outlined in the SoA (Section 1.3.1).

All eligible participants will continue their current SSRI/SNRI antidepressant (one only) at the same dose without change, which will be taken around the same time of the day as prior to entering the screening phase. Participants will receive OL adjunctive aticaprant 10 mg once daily starting on Day 1 (OL baseline) with the first dose taken on-site on Day 1.

Participants who respond (see Section 4.1.7 for definition of response) to adjunctive aticaprant (10 mg once daily) plus their current SSRI/SNRI after 6 weeks of treatment (EOP-I visit) may be eligible to proceed to the OL treatment stabilization phase. All participants who do not respond or do not proceed to the OL treatment stabilization phase will have an EW visit conducted and then enter the follow-up phase (Section 4.1.6); Visit 5.1 in the follow-up phase is their final study visit.

At the time the study is terminated, participants in the OL initial treatment phase will be given the opportunity to complete the phase (Week 6). At Week 6, these participants will have an EW visit conducted and then enter the follow-up phase (Section 4.1.6); Visit 5.1 in the follow-up phase is their final study visit.

### 4.1.4. Open-label Treatment Stabilization Phase

Evaluations that will be performed at each visit during this phase are outlined in the SoA (Section 1.3.1).

In this phase, the initial responders (after 6 weeks of treatment as defined in Section 4.1.7) will continue to receive OL adjunctive aticaprant (10 mg once daily) plus their current SSRI/SNRI for another 10 weeks to confirm the stable improvement in depressive symptoms.

All participants will continue their current SSRI/SNRI antidepressant (one only) at the same dose without change, which will be taken around the same time of the day as prior to entering the screening phase.

At Week 16, all eligible participants (both stable responders and participants who do not meet criteria for stable response) will proceed into the DB treatment maintenance phase. The last visit in the OL stabilization phase at Week 16 visit (Visit 3.5) will serve as first visit of the DB treatment maintenance phase (Visit 4.1 [see Section 4.1.5]).

Participants who prematurely discontinue during the OL treatment stabilization phase will have an EW visit conducted and then enter the follow-up phase (Section 4.1.6); Visit 5.1 in the follow-up phase is their final study visit.

At the time the study is terminated, participants in the OL treatment stabilization phase will be given the opportunity to complete the phase (Week 16). At Week 16, these participants will have

an EW visit conducted and then enter the follow-up phase (Section 4.1.6); Visit 5.1 in the follow-up phase is their final study visit.

### 4.1.5. Double-blind Treatment Maintenance Phase

Participants will enter the DB treatment maintenance phase from the OL treatment stabilization phase - Visit 3.5 (Week 16) of the OL treatment stabilization phase and Visit 4.1 (Week 16) of the DB treatment maintenance phase are performed on the same day. This phase will have a variable duration, continuing until the required number of relapse events have been achieved and the study is terminated (see Section 4.1.7 for the definition of relapse). Remote contact visits will occur every 2 weeks, on-site visits will occur every 4 weeks, and unscheduled visits (remote or on-site) will be conducted as needed to confirm relapse. Evaluations that will be performed at each visit during this phase are outlined in the SoA (Section 1.3.2).

After completion of all DB baseline assessments (Visit 3.5 [Week 16] assessments), eligible participants will enter the DB treatment maintenance phase (Visit 4.1).

- Participants who are stable responders (criteria will be blinded to sites; see Section 4.1.7) after a total of 16 weeks of treatment in the OL treatment phases, will be randomly assigned in a 1:1 ratio to receive adjunctive aticaprant 10 mg once daily or adjunctive placebo once daily during the DB treatment maintenance phase, while all participants continue their current SSRI/SNRI (one only) throughout the study.
- Additionally, since the criteria for stable response are blinded to the sites, participants who do not meet criteria for stable response at the end of the OL treatment stabilization phase will also proceed into the DB treatment maintenance phase using a sham randomization and will continue to receive adjunctive aticaprant 10 mg orally once daily plus their current SSRI/SNRI (one only). These participants will be analyzed separately for the efficacy analyses, and will be combined with the stable responder participants for the safety analyses.

All participants will take their first dose of DB study intervention at the site.

All participants will continue their current SSRI/SNRI antidepressant (one only) at the same dose without change, which will be taken around the same time of the day as prior to entering the screening phase.

Participants will continue in the DB treatment maintenance phase until they have a confirmed relapse (see Section 4.1.7) or the sponsor terminates the study once the required number of relapses have been achieved.

Participants who have a MADRS total score ≥22 at any time point during the DB treatment maintenance phase will have a consecutive MADRS assessment conducted separated by 7 (±3) days to confirm the relapse. If the relapse is not confirmed, participants will resume the regular visit schedule.

Participants who relapse may have the EMP visit conducted and then may proceed to the follow-up phase (see SoA in Section 1.3.3; Section 4.1.6). Participants who remain relapse-free at study termination and have completed their DB Week 4 visit will have an EMP visit conducted and then

enter the follow-up phase (Section 4.1.6). All randomized participants who have not yet completed the DB Week 4 visit in this phase when the study is terminated, will be encouraged to continue study intervention through DB Week 4 or at least complete assessments through the DB Week 4 visit. At DB Week 4, these participants will have an EMP visit conducted and then enter the follow-up phase of the study. For these participants (relapse or remain relapse-free at study termination), Visit 5.1 in the follow-up phase is their final study visit.

Participants who have not yet completed the DB Week 4 visit in this phase when the study is terminated and do not agree to complete assessments through DB Week 4 will have an EMP visit conducted and then enter the follow-up phase and have their final study visit (Visit 5.1).

Participants who have not relapsed and discontinue study intervention during the DB treatment maintenance phase for reasons other than withdrawal of consent will have an EW visit conducted and then enter the follow-up phase (Section 4.1.6).

### 4.1.6. Follow-up Phase

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 1.3.3).

**Follow-up Visit**

Participants should return to the study site for a follow-up visit within 14 (±7) days after an EW visit or the EMP visit. At the follow-up visit (Visit 5.1), safety and efficacy assessments/procedures will be completed per the SoA (Section 1.3.3).

Follow-up Visit 5.1 is the final study visit for participants who discontinue study intervention before the end of the OL initial treatment, OL treatment stabilization, or who have completed the OL initial treatment phase but are not eligible to continue to the OL treatment stabilization phase and for those participants who relapse during the DB treatment maintenance phase.

**Additional Follow-up Visits**

Participants who have not relapsed and discontinue study intervention during the DB treatment maintenance phase for reasons other than withdrawal of consent will be encouraged to continue with additional follow-up visits every 8 weeks per the SoA (Section 1.3.3) until they relapse or the study is terminated by the sponsor. The same criteria for relapse as described for the DB treatment maintenance phase will be applied to identify a relapse during the follow-up phase; questionable cases will be evaluated by the Independent Relapse Adjudication Committee.

### 4.1.7. Definition of Terms

**OL and DB Baseline:**

OL baseline is defined as Day 1 of the OL initial treatment phase, prior to the first dose of aticaprant.

DB baseline is defined as Day 1 of the DB treatment maintenance phase, prior to the first dose of study intervention (aticaprant or placebo) in this phase.

**OL Initial Treatment Phase Response**

Response is defined as ≥50% reduction in the MADRS total score from the OL baseline to the end of the OL initial treatment phase (Week 6).

**OL Treatment Stabilization Phase Stable Response**

To reduce potential site-based rater bias, this definition will be blinded to the site-based efficacy raters and documented outside the protocol.

**DB Treatment Maintenance Phase Relapse Criteria**

Depression relapse is defined as any of the following:

- MADRS total score ≥22 for 2 consecutive assessments separated by 7 days (±3-day visit window). The date of the second MADRS assessment will be used as the date of relapse.
- Hospitalization or observation for worsening of depression or any other clinically relevant event determined per clinical judgment to be suggestive of a relapse of depressive illness, such as active suicidal ideation with intent (ie, response of yes to C-SSRS item 4 or 5) or evidence of suicidal behavior based on the C-SSRS, suicide attempt, completed suicide, or hospitalization for suicide prevention. If hospitalized for any of these events, the start date of hospitalization will be used as the date of relapse. Otherwise, the date of the event will be used if the participant is not hospitalized.

In case more than 1 relapse criterion is met, the earlier date will be identified as the date of relapse for this participant.

For other questionable cases (ie, not fulfilling the above noted definitions), a blinded Independent Relapse Adjudication Committee will be established to determine if an event is a relapse event. If a discontinuation or change in antidepressant treatment (study intervention or current antidepressant) is made in the DB treatment maintenance phase for non-logistical/non-administrative reasons, but objective criteria for worsening depression as listed above are not met, the adjudication committee will determine if an event is a relapse event. Refer to Section 10.2.7 for details.

Note: The same criteria for relapse as described for the DB treatment maintenance phase will be applied to identify a relapse during the follow-up phase.

**Sexual Dysfunction Definitions Based on CSFQ-14:**

SDF is defined as a CSFQ-14 total score at OL baseline of ≤41 for female and ≤47 for male participants.

Improvement in SF is defined as an increase in the CSFQ-14 total score of ≥3 points.

## 4.2. Scientific Rationale for Study Design

Improving depression symptoms, with the goal of achieving and maintaining remission, is the key objective for the treatment of MDD (APA 2010; Bauer 2017). There is substantial evidence indicating that patients in remission have less functional impairment, better overall prognosis, and a lower suicide risk compared to patients who have responded to antidepressant therapy but continue to have residual depressive symptoms (Corey-Lisle 2004; Judd 1998; Romera 2010; Sakurai 2017). Since MDD is a chronic condition, maintenance treatment is recommended per treatment guidelines. CHMP guidelines for clinical trials in MDD require any new treatment to demonstrate that its short-term response can be maintained during the index depression episode (EMA Guideline on Clinical Investigation of Medicinal Products in the Treatment of Depression 2013). As mentioned in the introduction, while efficacy of adjunctive aticaprant in MDD has been evaluated in short-term studies, there have been no studies to date to assess whether the antidepressant effect of adjunctive aticaprant is sustained over the long term.

### 4.2.1. Study Population

In the seminal 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 2006). Suboptimal response to first-line standard-of-care antidepressant treatment for MDD remains a significant problem resulting in persistent impairment and high utilization of health care resources (Kennedy N 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 antidepressants and impeding remission or prolonging the time to remission (Uher 2012).

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

analysis will be conducted in adult participants with a diagnosis of MDD ANH+ who have achieved a stable response to initial treatment with aticaprant at the end of the OL treatment stabilization phase, and are randomly assigned to adjunctive aticaprant or adjunctive placebo in the DB treatment maintenance phase. The key secondary analysis will be conducted at Week 4 in the DB treatment maintenance phase in the subpopulation of adult MDD ANH+ participants with SDF at OL baseline who are stable responders with improvement in SF at the end of the OL treatment stabilization phase. Criteria defining stable response at the end of the OL treatment stabilization phase will be described in an addendum to the protocol which will be blinded to the study sites.

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

### 4.2.2. Blinding, Control, Intervention Groups

All participants will receive aticaprant 10 mg during the OL treatment phases. Criteria defining stable response at the end of the OL treatment stabilization phase are blinded to the sites and are provided in an addendum to the study protocol, as described in Section 4.1.7. Participants who are stable responders after a total of 16 weeks of treatment in the OL treatment phases, will be randomly assigned to receive adjunctive aticaprant 10 mg or adjunctive placebo in the DB treatment maintenance phase. Additionally, since the criterion for stable response is blinded to the sites, participants who do not meet criteria for stable response at the end of the OL treatment stabilization phase will also proceed into the DB treatment maintenance phase using a sham randomization and will continue to receive aticaprant 10 mg.

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

Activities employed to ensure independent confirmation of the diagnosis, severity of the depressive episode and adequacy of the current antidepressant treatment are described in Section 8.1.3.

### 4.2.3. Duration of OL Treatment Phases

The 6-week duration of the OL initial 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 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 OL initial treatment 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).

The additional 10 weeks of OL stabilization treatment following the OL initial treatment of 6 weeks is considered adequate based on findings from a prior study which reported a strong correlation between shorter initial treatment and greater relapse risk compared with longer initial treatment, supporting the benefits of a longer stabilization phase (Baldessarini 2015). This allows for a total OL treatment phase of 16 weeks.

### 4.2.4. Design of the DB Treatment Maintenance Phase

The purpose of the current study is to evaluate the ability of continued treatment with adjunctive aticaprant to maintain its overall antidepressant effect after participants achieve stable response. To that end, this study will assess the efficacy of aticaprant 10 mg once daily compared with placebo once daily as adjunctive therapy to an antidepressant in delaying relapse of depressive symptoms in adult participants with MDD ANH+ who have a stable response following the OL treatment with adjunctive aticaprant. The depression relapse criteria, described in Section 4.1.7, are similar to criteria used by other registration studies for relapse prevention with antidepressants (Borges 2014), all of which focus on identifying clinically significant worsening of overall depressive symptoms.

**Key Secondary Endpoint: Rationale for the Proposed Design**

The key secondary endpoint aims to assess the effects of aticaprant on SF in an adjunctive treatment paradigm, ie, when added to an SSRI/SNRI. The design of the study follows the recommendation for reducing potential bias of the underlying condition noted in the FDA consensus paper when assessing drug effects on SF in MDD (Khin 2015). Only the participants with MDD with SDF at OL baseline who achieve stable response and improvement of SF (at Week 16) will be included in the proposed efficacy analysis. This subset allows for assessing the effect on SF in an unbiased manner, because the participant's depression is under control with acute symptoms resolved (Week 6) and sufficient time (+10 weeks) given to demonstrate continued antidepressant effectiveness. This allows for the assessment of adjunctive aticaprant treatment on SF in a sample for which the underlying condition is stable for a sufficient duration and is not expected to confound the ability to assess the effects of aticaprant on SF in the DB treatment maintenance phase (DB Week 4).

The key secondary endpoint allows comparison between 2 active treatments: aticaprant plus SSRI/SNRI and SSRI/SNRI plus placebo, to demonstrate that continued treatment with aticaprant plus SSRI/SNRI is superior to SSRI/SNRI plus placebo in preventing the worsening of SF in participants whose MDD is under control (stable responders).

The duration of 4 weeks in the DB treatment maintenance phase for the assessment of this endpoint is considered sufficient to demonstrate worsening of SF/re-emergence of SDF in the SSRI/SNRI plus placebo group. Symptoms and complaints of SDF are known to develop rapidly with most SSRI/SNRIs. For example, in a study of a healthy adult cohort treated with paroxetine, the onset of SDF was observed as early as Day 4 upon treatment initiation, manifesting initially on the orgasm domain, followed by arousal dysfunction (Day 6) and desire (Day 8), and impairment in total SF by Day 15 following treatment initiation (Dunn 2007).

Based on the assumed 6-month relapse rates and discontinuation rates, it is expected that the proportion of participants who would discontinue prior to DB Week 4 is minimal (≤10%). Most participants who discontinue prior to DB Week 4 who have EW visits and follow-visits completed per protocol will have assessments completed within the DB Week 4 window and data will be available for the key secondary endpoint. Additionally, participants who have not yet completed the DB Week 4 visit in this phase when the study is terminated, will be encouraged to continue study intervention through DB Week 4 or at least complete assessments through DB Week 4.

### 4.2.5. 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/assent may be obtained through various sources (eg, paper or electronic such as eConsent, eSignature, or digital signature) as determined by regulations as well as study and/or patient preferences.

The probability of receiving placebo and the concept of random assignment will be explained to the participant. Only participants who have not adequately responded to their current antidepressant medication and continue to have moderate-to-severe depression and where a clinician would consider adding adjunctive treatment will be enrolled. Current antidepressant medication (SSRI/SNRI) will need to be continued at the same dose without change throughout the study and the study intervention will be added to it. Withdrawal and/or discontinuation symptoms for prohibited therapies may be challenging for some participants. 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.

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 104 mL, which is less than a Red Cross blood donation.

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

For participants who consent to the optional collection of real-world medical data, the sponsor is committed to protect their data and privacy. Tokenization and matching procedures will be utilized to allow for those participant's medical data to be obtained without violation of participant confidentiality. Participants will be informed that consent to this part of the study is completely optional and that they can withdraw their consent at any given time. In the event of withdrawal of consent, the sponsor will remove the token generated and any associated linked real-world data. Participation in or withdrawal from this optional part of the study will not affect the participation in the main study (see Section 8.7).

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

### 4.2.6. Biomarker Sample Collection

The primary goal of the biomarker analyses is to investigate an effect of biomarker status on maintenance of treatment response/relapse propensity. Secondary goals for the biomarker collections are to explore biomarkers reflective of the mechanism of action of aticaprant or that help to explain interindividual variability in efficacy, safety, or tolerability.

CCI [redacted]

[redacted]

### 4.2.7. 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 the 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, clinicaltrialsregister.eu, 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 sponsor will terminate the study once the required number of relapses have been achieved in the DB treatment maintenance phase. For participants who are ongoing in the OL initial treatment, OL treatment stabilization, and DB treatment maintenance phases when the sponsor terminates the study, details are provided in Section 4.1.3, Section 4.1.4, and Section 4.1.5, respectively, regarding study intervention and which visits should be performed.

> **Note:** The number of participants evaluable for SF will be monitored. In the event there is an insufficient number of participants evaluable for the key secondary endpoint, enrollment may continue until there are 182 participants evaluable for the key secondary endpoint or up to a maximum of 127 relapses have been reported for the primary endpoint.

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

See Section 10.2.15 for additional information on early termination of the study by the sponsor and early closure of a study site by the sponsor or investigator.

**Participant Study Completion Definition**

A participant will be considered to have completed the study if the participant completed the DB treatment maintenance phase (ie, had a relapse or is relapse-free in the DB treatment maintenance phase when the study is terminated).

Participants who prematurely discontinue study intervention for any reason other than a relapse or study termination in the DB treatment maintenance phase will not be considered to have completed the study. Any participant who prematurely discontinues study intervention during the OL treatment phases, is a non-responder at the end of initial OL treatment, or is ongoing in the OL treatment phases when the study is terminated will not be considered to have completed the study.

# 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 OL 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 and OL baseline 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 OL baseline (Visit 2.1 – assessed by the 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 the OL 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 OL 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, 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 OL 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 OL 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 OL baseline. The result of the OL baseline test for drugs of abuse must be negative for the participant to proceed with OL 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 OL baseline. The result of the OL baseline test 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 and Section 10.6 that would not permit dosing on Day 1 (ie, OL 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 (eg, drug or medication like SSRI/SNRI), by a medical condition (eg, 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 is 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 study until the last dose of study intervention.

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 numbers, 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 Interventions Administered

<table>
<tr><th>Designation</th><th>Product</th></tr>
<tr><td>Investigational Medicinal Product(s)</td><td>Aticaprant/JNJ-67953964<br><br>Authorization status in the EU/EEA:<br><br><table><tr><td>Authorized</td><td>-</td></tr><tr><td>Unauthorized</td><td>Aticaprant/JNJ-67953964</td></tr><tr><td>Unauthorized</td><td>Matching placebo</td></tr></table></td></tr>
<tr><td>AxMP</td><td>Current SSRI/SNRI antidepressant*<br><br>Authorization status in the EU/EEA:<br><br><table><tr><td>Authorized</td><td>citalopram<br>duloxetine<br>escitalopram<br>fluvoxamine<br>fluoxetine<br>milnacipran<br>levomilnacipran<br>paroxetine<br>sertraline<br>venlafaxine<br>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.

During the OL treatment phases, all participants will receive aticaprant 10 mg. During the DB treatment maintenance phase, participants who have a stable response will receive aticaprant 10 mg or placebo based on random assignment, or aticaprant 10 mg only by sham randomization for participants who do not meet criteria for stable response. During all phases, participants will receive 1 tablet to be taken orally once daily around the same time and preferably in the morning (with or without food).

The first dose of study intervention will be taken by the participant at the study site on Day 1 of the OL initial treatment phase and witnessed by the investigator or a properly trained designee. Thereafter, study intervention will be taken at home by the participant for daily self-administration until the next clinical site visit. For clinical site visits where blood samples for PK analysis will be collected (as indicated in the SoA [Section 1.3, Clinical Pharmacology Assessments]), participants will be asked not to take study intervention in the morning before they come to the site as the study intervention will be self-administered on-site and witnessed by the investigator or a properly trained designee. See Section 6.5 for information on measures that will be taken to ensure and document study intervention compliance.

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

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

All participants will continue their current SSRI/SNRI antidepressant (one only, the AxMP) at the same dose without change, which will be taken around the same time of the day as prior to entering the screening phase. The participant's use of their current SSRI/SNRI antidepressant therapy during the study should be captured by the participant using a medication diary (see Section 6.9.1).

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

**Description of Interventions**

| | **OL Initial Treatment Phase and OL Treatment Stabilization Phase and DB Treatment Maintenance Phase: Group/Arm A** | **DB Treatment Maintenance Phase: Group/Arm B** |
|---|---|---|
| **Intervention Name**[a] | Aticaprant/JNJ-67953964 | Placebo |
| **Type** | Drug | Drug |
| **Dose Formulation** | Film-coated tablet | Matching placebo tablet |

| | OL Initial Treatment Phase and OL Treatment Stabilization Phase and DB Treatment Maintenance Phase: Group/Arm A | DB Treatment Maintenance Phase: Group/Arm B |
|---|---|---|
| **Intervention Name**[a] | Aticaprant/JNJ-67953964 | Placebo |
| **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]<br><br>Child resistant | Individual participant blister kits[b]<br><br>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 Investigational Medicinal Products (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 Investigational Medicinal Products (aticaprant 10 mg or placebo).

**Intervention Allocation**

Central randomization will be implemented in this study for participants entering into the DB treatment maintenance phase. Separate randomization lists will be created for stable responders and for participants who do not meet criteria for stable response. As the criteria defining stable response are blinded to the study sites, the randomization list to which the participants belong will not be revealed to the study sites or the participants.

For the list pertaining to stable responders, participants will be randomly assigned to 1 of 2 intervention groups in a 1:1 ratio based on a computer-generated randomization schedule implemented in the IWRS before the study. The randomization will be balanced by using randomly permuted blocks and will be stratified by SF status, sex, and country/territory. The following 2 strata pertaining to SF status are defined: (i) presence of SDF at the beginning of the OL initial treatment phase and improvement in SF at the end of the OL treatment stabilization phase, (ii) absence of SDF at the beginning of the OL initial treatment phase or absence of improvement

in SF at the end of the OL treatment stabilization phase. 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.

A sham randomization list will be created for participants who do not meet criteria for stable response; all participants in this list will be administered adjunctive aticaprant 10 mg.

## 6.4. Blinding, Masking

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

Blinding procedures are applicable only to the DB treatment maintenance phase.

Stable responder participants will be randomly assigned to receive adjunctive aticaprant 10 mg or adjunctive placebo in the DB treatment maintenance phase. Participants who do not meet criteria for stable response will receive blinded aticaprant 10 mg in this phase. 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 data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

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

The date and time 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 should return for the EW and follow-up assessments as indicated in Section 4.1.5 and Section 4.1.6, respectively.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed. However, if an IA is performed, the randomization codes and the translation of randomization codes into intervention and control groups will be disclosed only to those authorized to handle unblinded data.

In rare circumstances when a potential safety issue that may impact the overall benefit-risk assessment of the IP 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

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

Except for specified on-site clinic visits, the study intervention will be self-administered by the participant at home daily around the same time and preferably in the morning during all phases of the study. The first dose will be taken on-site on Day 1 of the OL initial treatment phase and will be witnessed by the investigator or a responsible designee. For clinical site visits where blood samples for PK analysis will be collected (as indicated in the SoA [Section 1.3, Clinical Pharmacology Assessments]), study intervention will be self-administered on-site and witnessed by the designated study site personnel. Participants will receive instructions on compliance with the study intervention treatment. During the course of the study, the investigator or designated study site personnel will be responsible for providing additional instruction to re-educate any participant to ensure compliance with taking the study intervention. A participant diary will be provided to capture study intervention use and it will be reviewed by the investigator or designated study site personnel 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 subsequent study visits. Participants with repetitive noncompliance to the study intervention during the study (as defined in Section 7.1) may be withdrawn from study intervention. Missing study intervention doses due to temporary interruption (eg, AE per Section 7.1.3 or other clinically relevant reason) will not be considered noncompliance.

The investigator or designated study site personnel will maintain a log of all study intervention dispensed and returned. Drug supplies for each participant will be inventoried and accounted for throughout the study. If appropriate, additional details may be provided in a site IP 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 (in the DB treatment maintenance phase). No dose modifications in study intervention are permitted during the study.

## 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 following the end of the DB treatment phase, and that they should return to their primary physician to determine standard of care. 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.

## 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 sponsor's 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 proton pump inhibitors, $H_2$ blockers or other gastroprotective agents, NSAIDs, or aspirin, must be recorded (eg, dose, duration, reason) in the "Concomitant Therapy" CRF. Similarly, for people of childbearing potential (POCBP) ongoing 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 (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 OL baseline 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 study, all participants will need to continue their current SSRI/SNRI antidepressant (**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) on which they have had inadequate response at the time of screening.

The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. No changes in current antidepressant or dose are permitted from screening until the end of the DB treatment maintenance phase. Participants will receive instructions on compliance with their current oral antidepressant treatment (SSRI/SNRI). During the course of the study, the investigator or designated study site personnel will be responsible for providing additional 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 OL treatment phases and DB treatment maintenance 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 (see Section 1.3).

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

### 6.9.2. 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 until after the last dose of study intervention.

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 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 phases 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 maintenance 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

## 7.1. Discontinuation of Study Intervention

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

- The participant withdraws consent to receive study intervention (**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 EW visit and the follow-up phase, another reason for discontinuation of study intervention should be selected.)
- Lack of efficacy, per investigator's judgment (during the OL treatment phases only).[a]
- The participant does not meet response criteria for continuing into the OL treatment stabilization phase at the end of the OL initial treatment phase. Refer to Section 4.1.7.
- The sponsor terminates the study based on number of required relapse events achieved.
- 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:
  - AST and/or ALT >5 x ULN (at least twice over a 2-week period; refer to Section 7.1.1).
  - AST and/or ALT ≥3 x ULN and total bilirubin ≥2 x ULN (confirmed by repeat testing; refer to Section 7.1.1).
  - QTcF change from baseline is ≥60 msec AND QTcF >480 msec (refer to Section 7.1.2).
  - QTcF >500 msec (refer to Section 7.1.2).
- The participant becomes pregnant. Refer to Section 10.3.4.
- Noncompliance with study intervention administration defined as:
  - OL initial treatment phase: participant misses 4 consecutive doses (not eligible to continue to OL treatment stabilization).
  - OL treatment stabilization phase: participant misses 21 doses (not eligible for randomization).

[a] A participant who relapses during the DB maintenance phase is considered to have completed the study.

  - DB treatment maintenance phase will be assessed on a case-by-case basis.
- Major protocol deviation (assessed on a case-by-case basis).
- Study intervention blind is broken.
- Positive urine drug test for PCP or cocaine at any time point during the study.

For participants who discontinue study intervention before the end of the OL initial treatment, OL treatment stabilization, or DB treatment maintenance phase for reasons other than withdrawal of consent, or who have completed the OL initial treatment phase but are not eligible to continue to the OL treatment stabilization phase, an EW visit should be conducted, followed by the follow-up phase. If the EW visit occurs on the same day as a scheduled visit, the EW visit may be performed on the same day and duplicate assessments are not required. Please refer to Section 4.1.6 for additional information regarding the follow-up phase.

For participants who are ongoing in the OL initial treatment, OL treatment stabilization, and DB treatment maintenance phases when the sponsor terminates the study based on number of required relapse events achieved, details are provided in Section 4.1.3, Section 4.1.4, and Section 4.1.5, respectively, regarding study intervention and which visits should be performed.

Participants who relapse or remain relapse-free in the DB maintenance phase when the study is terminated are considered to have completed the study (see Section 4.4). These participants are not considered to have discontinued early from study intervention.

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

### 7.1.1. Liver Chemistry Stopping Criteria

Stopping of study intervention for abnormal liver tests is required by the investigator when either a participant meets ALT or AST elevations >5 x ULN at least twice over a 2-week period, AST and/or ALT ≥3 x ULN and total bilirubin ≥2 x ULN (confirmed by repeat testing), or one of the conditions outlined in Section 10.5, 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 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 do not apply at screening or prior to first dose at OL baseline, Day 1.

A participant who meets either of the following criteria (after first dose of study intervention at OL baseline, Day 1) 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 Interruption, Restart, or Rechallenge

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 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 before the end of the OL initial treatment, OL treatment stabilization, or DB treatment

maintenance phase, or who have completed the OL initial treatment phase but are not eligible to continue to the OL treatment stabilization phase 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. Please refer to Section 4.1.6 for additional information regarding the follow-up phase.

Participants who relapse or remain relapse-free in the DB treatment maintenance phase at the time when the sponsor terminates the study based on number of required relapse events achieved are considered to have completed the study; they are not considered an early withdrawal (see Section 4.4). Details are provided in Section 4.1.5 regarding study intervention for participants who are relapse-free and which visits should be performed.

**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, or withdrew due to lack of efficacy [OL treatment phases only]). 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 continue in the study 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**

If a participant discontinues from the study, an EW visit should be conducted within 1 week of the date of discontinuation, followed by the follow-up phase (Visit 5.1). Participants who prematurely discontinue study intervention for any reason other than relapse or study termination by sponsor before completion of the DB treatment maintenance phase will not be considered to have completed the study.

Missing data in clinical trials can lead to problems that undermine the scientific credibility of causal conclusions. The most common reason for missing data is participants who discontinue the assigned study intervention because of AEs, lack of efficacy (option in OL treatment phases only),

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 5.1).

Additionally, to reduce missingness of the key secondary endpoint data due to relapse, discontinuation of study intervention and/or current antidepressant, or study termination by the sponsor before DB Week 4, participants who have not yet completed the DB Week 4 visit when the study is terminated, will be encouraged to continue study intervention through DB Week 4 or at least complete assessments through the DB Week 4 visit.

### 7.2.1. Withdrawal From the Use of Research 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.

## 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.

# 8. STUDY ASSESSMENTS AND PROCEDURES

### Overview

The 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. To reduce the time spent by a participant on-site during the clinic visit, sites are recommended for clinic visits in the study treatment period with several procedures to consider scheduling and conducting the MADRS assessment (with videoconferencing) outside of the on-site visit.

> **Note:** At the EOP-S visit (Visit 3.5), the MADRS must be performed **before (**respecting the visit window) **or at the on-site visit**.

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, at OL baseline (Day 1) and other site visits with fasting blood sampling, this may not be possible and the following recommendations should be followed:

- At OL baseline (Visit 2.1, Day 1), MADRS, PROs, CGI-S, and C-SSRS must be completed prior to dosing. It is recommended that procedures should be performed in the following sequence: interview with qualified site-based rater (MADRS [SIGMA version], if not completed via videoconference before the actual visit) to confirm eligibility, blood samples and urine collection, breakfast, 12-lead ECGs, vital signs, PROs, CGI-S, C-SSRS, other safety assessments, followed by dosing.
- At all other site visits with fasting blood sampling for biomarker assessments, it is recommended that procedures should be performed in the following sequence: 12-lead ECGs, vital signs, blood samples and urine collection, dosing, breakfast, PROs, interview with qualified site-based rater (MADRS [SIGMA version], if not completed via videoconference before the actual visit; CGI-S), C-SSRS, and other safety assessments.
- Additional serum (by central laboratory) or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

The total blood volume to be collected from each participant will be approximately 104 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 | 3 | 12.0 |
| Biomarker samples (plasma and serum) | 20.0 | 3 | 60.0 |
| Approximate Total[c] | | 15 | 104.0 |

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. Total number of samples will depend on how long participants remain in study. Number of samples specified is through DB Week 12; for participants who remain in the DB treatment maintenance phase longer, additional blood samples will be collected every 12 weeks.
   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 if applicable) 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), CGI-S (depression), 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
- Engage: A Smartphone Application used for video and audio teleconferencing (where permitted)

  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. Audio recording (if applicable) 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 I 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, mental health professional, or trained rater 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 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).

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. 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.

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.

### 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. 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 2 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 scale score. In addition to providing a total sexual functioning score, the CSFQ-14 allows the possibility of subscale scores: 5 subscales - (i) Desire/Frequency, (ii) Desire/Interest, (iii) Arousal/Excitement, (iv) Orgasm/Completion, (v) Pleasure. Normal SF is defined as a CSFQ-14 total score at screening and OL 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

### 8.2.9. CCI

CCI

### 8.2.10. CCI

CCI

CCI

CCI [redacted]

### 8.2.11. Work Productivity and Activity Impairment: Depression (WPAI:D)

The WPAI:D questionnaire is a patient-reported instrument to measure impairments in both paid work and unpaid work (Reilly 1993). It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problems during the past 7 days.

## 8.3. Safety Assessments

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 OL 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 after the first dose of study intervention at OL baseline (Day 1), the average QTcF of three 12-lead ECGs, recorded 4 minutes apart, will be used to assess QTc stopping criteria (see Section 7.1.2, QTc Stopping Criteria).

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

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 acceptable 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 (ie, AESI in this study) 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/IECs/IRBs in each respective country/territory, as applicable.

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

The primary efficacy endpoint is depression relapse (see Section 4.1.7) and as such will not be reported as an AE.

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 10.3.3.1 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 samples of approximately 4 mL for the determination of plasma concentrations of aticaprant and any relevant metabolite(s) (if warranted) will be collected from participants as indicated in the SoA (see Section 1.3, Clinical Pharmacology Assessments).

The exact dates and times of PK blood sample collection must be recorded. Study intervention dosing time on the day before each PK sample collection will be accurately recorded by exact dosing date and time by the participant in the participant diary.

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

### 8.5.2. Analytical Procedures

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

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

### 8.5.3. Pharmacokinetic Parameters and Evaluations

**Parameters**

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

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

**Pharmacokinetic/Pharmacodynamic Evaluations**

The relationship between 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 CSFQ-14 total score.

The results of the PK-PD analyses will be performed and 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): (a) to explore effect of biomarker signature status on maintenance of effect/relapse propensity; (b) to explore biomarkers that help to explain interindividual variability in efficacy, safety, or 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.

Sample collection and testing will comply with local regulations.

## 8.8. Participant Medical Information Prior to, During and After the Study (Optional Real-world Data Collection – US Only)

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

## 8.9. Ongoing Participant Review

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

## 8.10. Immunogenicity Assessments

Not applicable.

## 8.11. Medical Resource Utilization and Health Economics

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

## 9.1. Statistical Hypotheses

The hypothesis of the study is that adjunctive aticaprant is superior to adjunctive placebo in delaying relapse of depressive symptoms in participants with MDD ANH+ who have had an inadequate response to treatment with an SSRI/SNRI and subsequently achieved stable response after OL treatment with adjunctive aticaprant. The null hypothesis is that there is no difference in survival functions between adjunctive aticaprant and adjunctive placebo groups during the DB treatment maintenance phase.

If $S_T(t)$ is the survival function for the adjunctive aticaprant 10 mg group and $S_P(t)$ is the survival function for the adjunctive placebo group, the hypotheses can be written as follows:

$H_0$: $S_T(t) = S_P(t)$ for all $t>0$
$H_1$: $S_T(t) \neq S_P(t)$ for some $t$

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 in favor of aticaprant 10 mg.

## 9.2. Analysis Sets

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

| Analysis Sets | Description |
|---|---|
| Enrolled | All participants who sign the ICF. |
| Full Analysis Set-Interim Analysis (FAS_IA) | All participants who have achieved stable response at the end of the OL treatment stabilization phase and who are randomized to receive study intervention in the DB treatment maintenance phase at the time of the IA data cutoff. |
| Full Analysis Set (FAS) | All participants who have achieved stable response at the end of the OL treatment stabilization phase and who are randomized to receive study intervention in the DB treatment maintenance phase. |
| Full Analysis Set-Sexual Function (FAS_SF) | All randomized stable responder participants with SDF at OL baseline who have improvement in SF at the end of the OL treatment stabilization phase. |
| Safety Analysis Set (for each phase) | All participants who take at least 1 dose of study intervention in the respective phase. |

The analysis of the primary endpoint will be based on the FAS. The analysis of the key secondary endpoint will be based on the FAS_SF. Analyses of efficacy data from the different phases

(OL initial treatment and OL treatment stabilization phases, and the DB treatment maintenance phase data collected from participants who do not meet criteria for stable response) and the corresponding analysis sets will be specified in the SAP.

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

## 9.3. Statistical Analyses

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

### 9.3.1. General Considerations

Participants who do not meet criteria for stable response will be analyzed separately for the efficacy analyses but will be combined with stable responders for the safety analyses.

### 9.3.2. Primary Endpoint/Estimand Analysis

The primary endpoint is the time from randomization into the DB treatment maintenance phase to the first documentation of a relapse event (as defined Section 4.1.7) in participants with MDD ANH+ who achieve a stable response at the end of the OL treatment stabilization phase.

**Primary Estimand:** The primary estimand is defined by the following:

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 shown a stable response to initial treatment with aticaprant and for whom continuing treatment would be clinically beneficial.

Endpoint: Time from randomization to the first documentation of a relapse event during the DB treatment maintenance phase.

Intercurrent Events: The following changes in study intervention and/or current antidepressant that have not been identified as a relapse by the adjudication committee will be managed using a hypothetical strategy (ie, as if the ICE did not occur):

- Discontinuation of study intervention only
- Discontinuation of both study intervention and current antidepressant
- Switch of study intervention only
- Switch of current antidepressant only
- Switch of both study intervention and current antidepressant

Consistent with the hypothetical strategy, the ICEs will be considered as censored in the analysis of the primary endpoint.

Summary Measure: Difference in the survival functions between treatment groups (Hazard ratio for the treatment effect – adjunctive aticaprant vs adjunctive placebo; log-rank test for the p-value).

Two supplementary estimands will be defined for the primary endpoint:

Supplementary Estimand 1: All components of the estimand are the same as the primary estimand except for the strategy of handling the ICEs, where composite strategy will be implemented, ie, all ICEs will be considered as a relapse.

Supplementary Estimand 2: All components of the estimand are the same as the primary estimand except for the strategy of handling the ICEs, where treatment policy strategy targeting the effect of treatment assignment regardless of the occurrence of the ICEs will be implemented.

The analyses for the primary endpoint will be carried out on the FAS. The primary efficacy endpoint will be the time between randomization into the DB treatment maintenance phase and the first documentation of a relapse event. Participants who meet at least 1 of the relapse criteria or are deemed by the independent adjudication committee to have a relapse for the primary analysis while receiving study intervention in the DB treatment maintenance phase by the time the study is terminated are considered to have had a relapse. All other randomized participants who have entered the DB treatment maintenance phase but do not have a relapse by the time the study is terminated will be considered censored.

The cumulative distribution function of the time to relapse will be estimated by the Kaplan-Meier method. Time to relapse will be summarized (number of relapse events, number of censored participants, median, 25th and 75th percentile of time to relapse, if estimable) by study intervention group. The primary analysis of study intervention differences will be conducted using an unstratified log-rank test. If an IA for event re-estimation is conducted, the final analysis will be based on a weighted combination test, which defines the test statistic as a weighted sum of the Stage 1 (before the IA) and Stage 2 (after the IA) test statistics. The estimate of the hazard ratio and its 95% CI will be based on the Cox proportional hazards model with study intervention as a factor. Relapse rates will be summarized by study intervention group.

For the log-rank test, delta adjustment with a tipping point will be conducted as a sensitivity analysis.

### 9.3.3. Key Secondary Endpoint/Estimand Analysis

The key secondary endpoint is the change in SF (measured by CSFQ-14) from DB baseline to end of Week 4 of the DB treatment maintenance phase in MDD ANH+ stable responder participants with SDF at OL baseline who have improvement in SF after OL treatment (16 weeks) with adjunctive aticaprant.

**Key Secondary Estimand:** This estimand is defined by the following components:

Study Intervention: same as the primary efficacy estimand.

Population: Patients with a diagnosis of MDD ANH+ with SDF who have shown a stable MDD response and improvement in SF to initial treatment with aticaprant and for whom continuing treatment would be clinically beneficial.

Endpoint: Change in CSFQ-14 total score from the DB baseline to the end of Week 4 of the DB treatment maintenance phase.

Intercurrent Events: The list of ICEs is the same as those for the primary estimand. The ICEs will be addressed with the treatment policy strategy, targeting the effect of treatment assignment regardless of the occurrence of these ICEs.

Summary Measure: Difference in means between treatment groups.

The analysis for the key secondary endpoint will be carried out on the FAS_SF. Change from the DB baseline to Week 4 of the DB treatment maintenance phase in CSFQ-14 total score will be analyzed by a Mixed-effect Model for Repeated Measures (MMRM). The fixed terms included in the model will be intervention group (adjunctive aticaprant 10 mg and adjunctive placebo), sex, country/territory, time, and time-by-intervention interaction, and CSFQ-14 total score at the DB baseline as a covariate. The within-subject covariance between visits will be estimated via an unstructured variance-covariance matrix. The Kenward-Roger method will be used for approximating the denominator degrees of freedom. In case of convergence problems with the default Newton Raphson algorithm, alternative approaches will be tried in the following order before using a structured variance-covariance matrix: Fisher scoring algorithm, and factor analysis structure. If 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 estimator will be used if a structured covariance matrix is implemented. Comparison between adjunctive aticaprant 10 mg and adjunctive placebo at Week 4 of the DB treatment maintenance phase will be performed using the appropriate contrast. Difference in LS means and 2-sided 95% CIs will be presented. Missing data will be imputed using unconditional reference multiple imputation method.

*Justification of unconditional multiple reference multiple imputation for missing data:* Strategies to minimize missing data either due to discontinuation or due to competing risk (ie, participants who relapse before Week 4) will be implemented (as presented in Section 7 of the protocol under *Managing Missing Data* subheading) with a goal to capture CSFQ assessments at Week 4 regardless of relapse or discontinuation of study intervention and/or antidepressant. This will enable implementation of treatment policy to handle the intercurrent events.

For participants who don't return for evaluations, missing data for the key secondary endpoint will be imputed using unconditional multiple imputation method. Under this approach, participants

from the aticaprant group are considered as not being treated any longer (and therefore similar to placebo participants) and participants from the placebo group are considered to have trajectories similar to those from their own study intervention arm who remained on study intervention. The imputed values would be sampled from the distribution of values in the control arm without accounting for the available post-baseline values prior to discontinuation in the imputation model. This strategy effectively discards partial data collected prior to drop out and would not take into account any partial clinical benefit from a limited exposure to aticaprant. This method has been initially referred to as jump to reference (J2R) (Ratitch et al., 2013, O'Kelly & Ratitch, 2014) and then referred later as unconditional reference (Keene et al, 2014) so it can be distinguished from other ways of implementing a J2R method, such as J2R implemented via joint modeling or via stepwise imputation on previous residuals (DIA Scientific Working Group)

**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 a 2-sided 0.05 level accounting for multiplicity due to the primary (time to relapse of depression) and the key secondary (change in CSFQ-14 total score) efficacy endpoints. The testing procedure will first test the primary endpoint at 2-sided 0.05 level. If the hypothesis corresponding to the primary endpoint is rejected, then the key secondary endpoint will be tested at 2-sided 0.05 level; if the hypothesis corresponding to the primary endpoint is not rejected, then the key secondary endpoint cannot be formally tested.

**Secondary Efficacy Endpoints:**

For stable responders (FAS), treatment comparison between adjunctive aticaprant and adjunctive placebo in the change from DB baseline to endpoint in MADRS total score and CCI total score during the DB treatment maintenance phase will be performed using an analysis of covariance model with country/territory and study intervention as factors and DB baseline value as a covariate. LS estimates of the treatment differences and 95% CIs will be presented.

The analyses for other efficacy endpoints and study phases will be described separately in the SAP. To evaluate the consistency of efficacy in subgroups of participants, the analysis of primary and key secondary endpoints will be performed by intrinsic (baseline demographics) and extrinsic (baseline disease characteristics, medical history, baseline medications, etc.) factors.

### 9.3.4. Safety Analyses

All safety data will be analyzed separately for each phase based on the Safety Analysis Set specific to the phase, which consists of all participants who take at least 1 dose of study intervention in the respective phase.

**Adverse Events**

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the 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 AEs will be included in the analysis.

For each TEAE 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 intervention group. SAEs will be summarized separately.

AEs occurring during the follow-up phase will be summarized separately.

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

**Clinical Laboratory Tests**

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

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

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

**Electrocardiogram**

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

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

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

**Vital Signs**

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

**C-SSRS**

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

### 9.3.5. Other Analyses

#### 9.3.5.1. Pharmacokinetic Analyses

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 all individual plasma PK concentrations.

Available plasma concentration data for all participants will be provided in listings.

#### 9.3.5.2. Exploratory Biomarkers Analyses

The exploratory serum, plasma biomarkers will be tabulated by treatment and summary statistics will be calculated. Changes in exploratory biomarkers over time will be summarized by treatment group. Biomarker levels at baseline will be combined in multivariate models (biosignatures) and an effect of biosignature status on maintenance of effect/relapse propensity will be explored. Associations between baseline biomarker levels and clinical endpoints, such as change in MADRS, may be explored. Results may be presented in a separate Biomarker Report.

#### 9.3.5.3. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between 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 CSFQ-14 total score.

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

#### 9.3.5.4. Benefit-risk Analyses

Benefit-risk assessment for aticaprant 10 mg versus placebo as adjunctive therapy to an antidepressant (SSRI or SNRI) in participants with MDD ANH+ will be assessed using a structured framework approach. Benefit-risk assessment will be in the DB treatment maintenance phase. Benefits in the assessment will include endpoints for the symptoms of depression (eg, relapse, MADRS total score), symptoms of anhedonia (eg, CCI total score) and SF (eg, CSFQ-14). Assessment of risk will include clinically meaningful AEs, including TEAEs and AESIs such as CCI CCI 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

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

An IDMC will review the IA results. Additional details on the IDMC are provided in Section 10.2.7.

## 9.5. Sample Size Determination

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

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

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

It is anticipated that out of the 330 participants randomized in the DB treatment maintenance phase, approximately 182 participants will be evaluable for the assessment of SF. If the hypothesis for the primary endpoint is rejected, the study is powered at 80% to detect an effect size of 0.44 for the change in CSFQ-14 total score at Week 4 in the DB treatment maintenance phase.

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

# 10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1. Appendix 1: Clinical Laboratory Tests

The following tests will be performed according to the SoA 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 CRF or laboratory requisition form.

**Protocol-required Safety Laboratory Assessments**

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count<br>Red blood cell count<br>Hemoglobin<br>Hematocrit</td><td><u>RBC Indices:</u><br>MCV<br>MCH<br>% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u><br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils</td></tr>
<tr><td colspan="3">Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.<br><br>Note: An optional/ad-hoc assessment of INR will be performed by the central laboratory in case of liver function parameters elevation.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium<br>Potassium<br>Chloride<br>Bicarbonate<br>Blood urea nitrogen (BUN)<br>Creatinine<br>Glucose (in fasting condition when possible)<br>Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic (SGOT)<br>Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic (SGPT)<br>Gamma-glutamyltransferase (GGT)</td><td>Total bilirubin and Direct bilirubin<br>Alkaline phosphatase (ALP)<br>Creatine phosphokinase (CPK)<br>Uric acid<br>Calcium<br>Phosphate<br>Albumin<br>Total protein<br>Cholesterol (in fasting condition)<br>• Total cholesterol<br>• LDL-cholesterol<br>• HDL-cholesterol<br>Triglycerides (in fasting condition)<br>Magnesium</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.5.<br><br>Potential Hy's Law Case (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]) reporting requirements are defined in Section 8.4.1.</td></tr>
</table>

| Laboratory Assessments | Parameters | |
|---|---|---|
| Routine Urinalysis | Dipstick<br>Specific gravity<br>pH<br>Glucose<br>Protein<br>Blood<br>Ketones<br>Bilirubin<br>Urobilinogen<br>Nitrite<br>Leukocyte esterase | Sediment (if initial result is abnormal)<br>Red blood cells<br>White blood cells<br>Epithelial cells<br>Crystals<br>Casts<br>Bacteria |
| | If initial result is abnormal, flow cytometry will be used to measure sediment. In case of discordance between the initial results and the flow cytometric results, the sediment will be examined microscopically. | |
| Other Tests (at Screening, Baseline, or During Treatment) | • Serum or urine pregnancy testing for female participants of childbearing potential only.<br><br>**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 or local requirements.<br><br>• Urine drug test for drugs of abuse (eg, opiates [including methadone], cocaine, amphetamines, methamphetamines, cannabinoids, cannabidiol [CBD], PCP, barbiturates, or 3,4-methylenedioxymethamphetamine [MDMA]). 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.<br><br>• In some countries/territories, a urine or blood sample may be collected as an optional way to assess compliance with current antidepressant medications.<br><br>• TSH (screening only) for any participants with a history of thyroid disease or any participant (regardless of thyroid history), if the TSH value is out of range, a $FT_4$ 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.<br><br>• FSH (female participants only, at screening only if required for documentation that a female participant is not of childbearing potential, see Section 10.4).<br><br>• HbA1c.<br><br>• 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). | |

## 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.

GCP 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 collection of real-world data (US only): Approval for the collection of optional research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

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

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study intervention

- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

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

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

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

**Country/Territory Selection**

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.5.

**Other Ethical Considerations**

For study-specific ethical design considerations, refer to Section 4.2.5.

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

### 10.2.4. 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.

Refer to Recruitment and Informed Consent Procedure Template for details.

### 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 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

**Independent Data Monitoring Committee**

An IDMC will be commissioned to periodically review safety data. Additionally, the IDMC will review the IA results. After the safety reviews, the IDMC will make recommendations regarding the continuation of the study, or in the case of the IA, to adjust the number of relapses to achieve the desired power while maintaining the overall Type I error. The IDMC will consist of at least 1 medical expert in the relevant therapeutic area and at least 1 statistician. The IDMC responsibilities, authorities, and procedures will be documented in its charter.

**Adjudication Committee**

A blinded Independent Relapse Adjudication Committee will be established to determine if an event is a relapse event. The adjudication committee 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 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.

The summary of the results from the interim analysis, as described in Section 9.4, will be submitted to the EU along with the final CSR.

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:

- Race
- 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, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site 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. This data is 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 IP. 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 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 SSRI or 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?
  - Rechallenge: 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).

#### 10.3.3.1. Guidance for Assessing Severity of Adverse Events of Special Interest

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

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  - [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 OL 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 (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 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, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.4.5, Pregnancy and Appendix 3: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

**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 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 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**<br>**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)*<br>*(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**<br>**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<br>– oral<br>– intravaginal<br>– transdermal<br>– injectable |
| • Progestogen-only hormone contraception associated with inhibition of ovulation<br>– oral<br>– injectable |
| • Sexual abstinence<br>*(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)* |
| **NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)** |
| • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. |
| • Male or female condom with or without spermicide[b] |
| • Cap, diaphragm, or sponge with spermicide |
| • A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) |
| • 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).

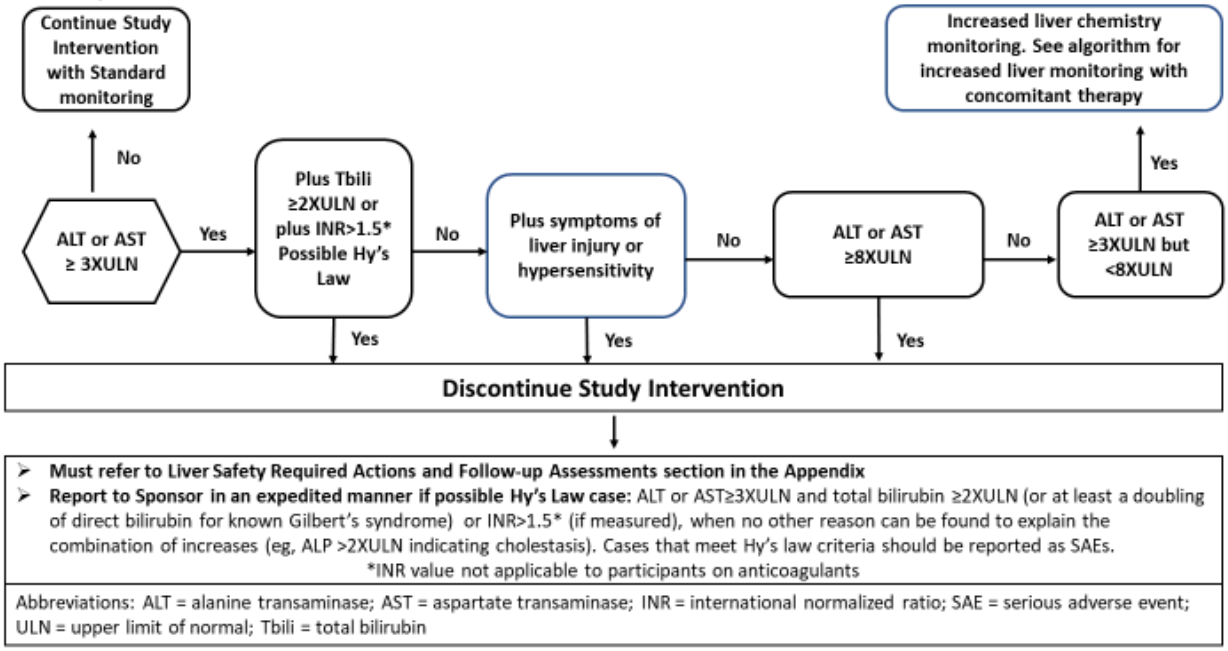
## 10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

### 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<br>OR<br>ALT or AST - ≥3 x 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<br>• Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, total bilirubin) until the abnormalities resolve, stabilize, or return to baseline<br>• If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 10.5.1.<br>• 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<br>• 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. For example, not all antibiotics within the listed classes may be excluded; specific cases may be discussed with the Medical Monitor, prior initiating a medication listed below.

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 until after the last dose of study intervention.

Of note, for any concomitant medication that is not listed below but has the potential to be a strong 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] are excluded. - Others with CCI [redacted] and CC [redacted] inhibition potential, used for other indication than MDD | CCI [redacted] |

| Drug Class | Episodic Use (PRN) | Continuous Use | Comments | Reason for Prohibition |
|---|---|---|---|---|
| | | | and limited period, are allowed. Consult with Medical Monitor before use.<br>- 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 starting on the day of the first dose of study intervention).<br>- 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.<br>- 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 [redacted] |
| 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 are prohibited from 1 injection cycle prior to first dose of study intervention. | |

| Drug Class | Episodic Use (PRN) | Continuous Use | Comments | Reason for Prohibition |
|---|---|---|---|---|
| Antivirals: NNRTI | N | N | | CCI [redacted] |
| 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 | - For continuous use: Only participants taking these medications at study entry can continue these medications.<br>- No dose increases "beyond the equivalent of 4 mg/day of lorazepam" or new benzodiazepine medications are permitted during screening and until the last study visit. New benzodiazepine restriction not applicable for episodic use. | |
| 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. | |

| Drug Class | Episodic Use (PRN) | Continuous Use | Comments | Reason for Prohibition |
|---|---|---|---|---|
| Crizotinib | N | N | | CCI |
| Dopamine Receptor Agonists (not listed elsewhere) | N | N | | |
| 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 | With sponsor approval, brief treatment with opiates may be allowed for treatment of acute injuries, etc. | |
| 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. | |
| Trazodone | N | N | Not allowed even if used for other | |

| Drug Class | Episodic Use (PRN) | Continuous Use | Comments | Reason for Prohibition |
|---|---|---|---|---|
| | | | 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.
- If paper PRO assessments, instruct participants to complete 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 | 27-Jun-2024 17:16:43 (GMT) | Document Approval |