

Janssen Research & Development***Clinical Protocol**

**An Open-label, Long-term, Safety and Efficacy Study of Aticaprant as Adjunctive Therapy
in Adult and Elderly Participants With Major Depressive Disorder (MDD)**

**Protocol 67953964MDD3003 VENTURA-LT; Phase 3
Version: Amendment 2****JNJ-67953964 Aticaprant**

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

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Amendment 2	22-Feb-2023
Amendment 1	08-Sep-2022
Original Protocol	23-Apr-2022

Amendment 2 (22 February 2023)

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

The changes made to the clinical protocol 67953964MDD3003 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendments are listed in Section 10.10. Appendix 10: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1. Synopsis, Overall Design; 4.1.2. Screening Phase; 5.1.2. Direct-entry Participants	Revised Inclusion Criterion 7: Have had an inadequate response to at least 1 ~~but no more than 3 antidepressants~~ oral antidepressant treatment (see the inclusion criterion below), administered at an adequate dose (at or above the minimum therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current episode of depression. An inadequate response is defined as <50% reduction in depressive symptom severity but with some improvement (> 0%) ~~during the current antidepressant trial~~ (ie, there may be minimal ~~some minor~~ to moderate symptomatic improvement since the initiation of treatment, but some of the initial symptoms are still present, troubling to the participant and affecting behavior and function) as assessed by the MGH ATRQ. ~~An adequate duration is defined as an antidepressant treatment for at least 6 weeks on a stable dose at or above the minimum therapeutic dose specified in the MGH ATRQ.~~ This must also apply to the participant's current antidepressant treatment.	Definition for inadequate response to the current antidepressant (SSRI/SNRI) is updated based on major Health Authority feedback to include MDD participants with >0% to <50% improvement to the current antidepressant based on the MGH ATRQ criteria for amount (%) of improvement. The updates allow inclusion of a broader MDD population for whom an add-on strategy is considered a viable treatment option following inadequate response to a standard of care antidepressant. Additionally, the upper limit of up to 3 inadequate antidepressants is removed to allow enrollment and evaluation of adjunctive aticaprant in participants with MDD with inadequate response to later lines of antidepressants.
1.1. Synopsis, Objectives and Endpoints; 3. Objectives and Endpoints	Revised definition of remission of depressive symptoms to a MADRS total score of ≤ 10 .	Update is made to align with the more commonly used cut off for defining remission using MADRS total score.
1.1. Synopsis, Objectives and Endpoints; 3. Objectives and Endpoints	Revised safety endpoint for ASEX to proportion of participants with clinically relevant sexual dysfunction.	To align the endpoint with the approach that the instrument developer recommends for analysis of the ASEX and to provide better analysis for the

Section Number and Name	Description of Change	Brief Rationale
		assessment of presence or absence of sexual dysfunction.
1.2. Schema; 4.1.1. Study Intervention(s); 4.1.2. Screening Phase; 4.1.3. Open-label Treatment Phase; 6.1. Study Intervention(s) Administered 6.8.1. SSRI/SNRI Antidepressant Therapy	Revised text to allow flexibility in oral SSRI/SNRI treatment, moved details for oral SSRI/SNRI treatment from Section 4.1.3 to Section 6.8.1, and updated cross-references from Section 4.1.3 to Section 6.8.1.	Update is made to reflect the flexibility in oral SSRI/SNRI treatment for participants in the OL study and to provide detailed information in the appropriate section of the protocol.
1.1. Synopsis, Number of Participants; 4.2.1. Study Population	Added text to clarify criteria for defining MDD ANH+ and MDD ANH- are blinded to the study sites and will be provided in an addendum to the study protocol.	To clarify criteria for defining MDD ANH+ and MDD ANH- are blinded to the study sites.
1.1. Synopsis, Statistical Methods, Sample Size Calculation; 1.1. Synopsis, Statistical Methods, Interim Analysis; 1.2 Schema; 4.2.1 Study Population; 9.2. Sample Size Determination; 9.5. Interim Analysis	Revised language with regards to China's and Japan's participation in the study.	To clarify that Japan's participation is optional in the study.
1.3. Schedule of Activities	Added assessments for evaluation of SSRI/SNRI antidepressant treatment for Transferred-entry participants Added assessment at Visit 2.14 (EOT/EW) under evaluation antidepressant compliance.	To add a missing assessment.
2.2.2.1. Human Pharmacokinetics	Additional information added to Human Pharmacokinetics section.	To add new information from completed clinical pharmacology studies.
4.1.1. Study Intervention(s)	Added text to clarify transferred-entry participants will not be unblinded before starting OL aticaprant treatment.	To clarify treatment assignment from the short-term studies MDD3001 and MDD3002 will remain blinded until the database lock of the short-term study.
4.2.4. Study-Specific Ethical Design Considerations; 8. Study Assessments and Procedures	Updated blood volume to be collected from each participant and revised footnotes in blood volume table to clarify sample collection.	Blood volume collected in the study was updated to include samples for antidepressant compliance. Footnotes were modified to clarify sample collection.
5.1.2. Direct-entry Participants	Revised Inclusion Criterion 8: Is currently receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms at screening, in any approved formulation and available in the participating country/territory: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine at a stable dose (at or above the minimum a therapeutic dose per MGH	Clarification made to improve understanding of the definition of "stable dose" for the current SSRI/SNRI antidepressant. Some text is removed as the information is captured in Inclusion Criterion 7.

Section Number and Name	Description of Change	Brief Rationale
	ATRQ) for at least 6 weeks. ~~and with some minor to moderate symptomatic improvement ($\geq 25\%$)~~ . The current antidepressant cannot be the first antidepressant treatment for the first lifetime episode of depression.	
5.2.2. Direct-entry Participants	Revised Exclusion Criterion 6 to exclude participants who have had no response/treatment failure to 5 or more antidepressant treatments including the current SSRI/SNRI.	Criterion is updated following feedback from a major health authority to broaden the study population and ensure exclusion of participants with a level of treatment resistance who are unlikely to benefit from an adjunctive treatment strategy.
5.2.2. Direct-entry Participants	Revised Exclusion Criterion 12 to exclude participants with an inadequate response to adequate course of treatment with intravenous or intranasal ketamine or esketamine; electroconvulsive therapy (ie, at least 7 treatments), vagal nerve stimulation, or deep brain stimulation device during the current episode.	Criterion is updated to better align with the study population and ensure exclusion of participants with non-response to treatment strategies in the ongoing episode who are unlikely to benefit from an adjunctive treatment strategy.
5.2.2. Direct-entry Participants	Added clarifying text to Exclusion Criterion 19 to specify on-site drug testing and clarify retesting is only permitted for stated reasons. Added text to clarify that a positive test for both cannabis and/or alcohol can lead to exclusion from the study.	To improve understanding of this criterion.
1.1. Synopsis, Statistical Methods	Added text describing the interim analysis.	For completeness and consistency with Section 9.5.
1.1. Synopsis, Objectives and Endpoints; 1.1 Synopsis, Statistical Methods, Safety Analyses; 1.3. Schedule of Activities; 3. Objectives and Endpoints; 8.3.10 Physician Withdrawal Checklist, 20-item (PWC-20); 9.4.1.7. PWC-20; 11. References	Added PWC-20 assessment at Visit 2.14 (EOT/EW) and Visit 3.1 (FU).	To add assessment and reference.
1.3. Schedule of Activities	Replaced “video” teleconferencing with “audio” teleconferencing for HDRS-17.	To correct an error.
1.3. Schedule of Activities	SHAPS assessments were added at Visits 2.2, 2.3, 2.5, 2.6, 2.8, 2.9, 2.11, 2.12, Unscheduled Visits, and Visit 3.1 (Follow-up).	To match with the CCI
1.3. Schedule of Activities, footnote “y”	Added footnote “y” to assessments required to be completed at Visit 2.1 (Baseline) prior to dosing.	To clarify assessments required to be completed at Visit 2.1 prior to dosing.
2.1. Study Rationale; 4.2.1. Study Population	Removed “core” from text describing symptoms persisting in patients treated with current antidepressants.	To align text with DSM-5 criteria.

Section Number and Name	Description of Change	Brief Rationale
6.4. Study Intervention Compliance	Clarifications were made regarding missed doses and non-compliance with study intervention.	Missed doses due to temporary interruption for clinically relevant reasons (eg, adverse event, etc) are not considered non-compliance with the study intervention.
6.8. Concomitant Therapy	Revised text to clarify that the 6 months prior to Screening applies to all of the listed medications. Added text to recommend that participants who receive an approved or authorized vaccine should do so at least 5 days prior to the start of dosing.	To clarify recording the medications used in past 6 months and to clarify recommended timing of vaccinations prior to dosing.
1.3. Schedule of Activities, Footnote “g”; 5.1.2. Direct-entry participants Criteria 7 and 8; 6.8.1. SSRI/SNRI Antidepressant Therapy	Added instructional text to clarify methods to confirm compliance to ongoing antidepressant treatment during screening and the OL Treatment Phase.	To provide further clarity to the sites about acceptable means of evaluating during study compliance to SSRI/SNRI antidepressant treatment.
6.8.2. Prohibited Therapies	Deleted last bullet.	To remove a duplication.
7.1. Discontinuation of Study Intervention; 7.2. Participant Discontinuation/Withdrawal from the Study	Revised criteria for discontinuation of study intervention and participant discontinuation from the study to align Phase 3 studies.	To provide consistency across the Phase 3 studies and to remove reasons for discontinuation of study intervention for which study participants will not be automatically withdrawn.
7.2.2. Withdrawal From the Use of Research Samples	Deleted the first paragraph.	To remove duplicate text.
8. Study Assessments and Procedures	Removed footnote “c” from biomarker samples in the blood volume table.	Footnote “c” is not applicable to biomarker samples.
8. Study Assessments and Procedures	Removed duplicate text.	To remove duplication.
8.1.3. Snaith-Hamilton Pleasure Scale	Revised the description of the scale to align with the Phase 3 studies.	To provide consistency across the Phase 3 studies.
1.3. Schedule of Activities, footnote “q”; 8.3.3. Electrocardiograms	Added text to clarify that triplicate ECGs are only required during screening if the QTcF is prolonged on the initial ECG or during OL Treatment phase in case of abnormality.	To clarify when triplicate ECGs are required.
8.3.7. Columbia Suicidality Severity Rating Scale	Corrected time to be recorded in the eCRF for suicidal ideation and/or suicidal behavior at screening.	Suicidal ideation in the past 3 months and/or suicidal behavior in the past 6 months are being collected in the eCRF.
8.3.8. Arizona Sexual Experiences Scale (ASEX)	Revised description of the ASEX to align with the revised safety endpoint.	Alignment edits.
8.4.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events	Deleted section.	This is a single arm, open-label clinical study so anticipated events will be assessed by the Safety Monitoring Team.
8.4.6. Adverse Events of Special Interest	Deleted text related to moderate/severe AESI in the reporting instructions. Added link to new appendix with guidance to investigators for assessing the severity of AESI.	To clarify that all AESI are to be reported and additional information to be collected on all cases.

Section Number and Name	Description of Change	Brief Rationale
8.5.1. CCI [REDACTED]	Added CCI [REDACTED]	To include CCI [REDACTED]
8.5.3. CCI [REDACTED]	Added CCI [REDACTED] and CCI [REDACTED] to list of measures of the CCI [REDACTED]	To add missing measures.
9.3. Participant Analysis Sets	Revised “Enrolled” to “All Participants” in the table describing analysis sets.	To clarify that the term ‘All Participants’ pertains to all screened participants.
9.4.3. Biomarker Analyses	Revised description of digital biomarker analyses.	To clarify digital biomarker analyses.
10.2. Appendix 2: Clinical Laboratory Tests	Revised bullet 3 under Other Tests (at Screening, Baseline, or During Treatment) to clarify that in some countries a urine or blood sample may be collected to assess compliance with current antidepressant medications.	To clarify that this sample is not required.
10.3.5. Long-term Retention of Samples for Additional Future Research	Added a sentence to define the start of the retention period.	To clarify when the long-term retention period begins.
10.4.3.1. Guidance for Assessing Severity of Adverse Events of Special Interest; 11. References	Added a new appendix to provide guidance to investigators for assessing the severity of AESI.	To provide recommendations to consider when assessing the severity of CCI [REDACTED] and CCI [REDACTED]
10.8. Appendix 8: Prohibited Concomitant Therapies	Added barbiturates to list of prohibited therapies and removed anxiolytics except buspirone.	To clarify that barbiturates are not permitted. To clarify that some anxiolytics are permitted, but buspirone remains a prohibited medication.
10.7.2. Guidance Specific to this Protocol, Data Collection	Revised bullet for missed doses to remove reference to removal of dosing form.	To correct the procedure for recording missed doses due to COVID-19.
1.1. Synopsis, Safety Evaluations; 1.1 Synopsis, Statistical Analysis; 1.3. Schedule of Activities; 4.1.3. Open-label Treatment Phase; 8. Study Assessments and Procedures; 8.3.9. Mini Mental State Examinations (MMSE); 8.9. Participant Medical Information Prior to, During and After the Study (Optional Real-world Data); 9.4. Statistical Analyses	Minor text edits and clarifications were made for alignment.	To provide consistency within the document.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

An Open-label, Long-term, Safety and Efficacy Study of Aticaprant as Adjunctive Therapy in Adult and Elderly Participants With Major Depressive Disorder (MDD)

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

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

The present study is being conducted to investigate the long-term safety and tolerability of daily aticaprant as adjunctive therapy to current antidepressant treatment (with a selective serotonin uptake inhibitor [SSRI] or a serotonin and norepinephrine reuptake inhibitor [SNRI]) in adult participants (18 to 74 years, inclusive) with MDD who have had an inadequate response to antidepressant therapy with an SSRI or SNRI in the current depressive episode. Additionally, the study will investigate the long-term efficacy of aticaprant as adjunctive therapy to an antidepressant (SSRI/SNRI) in adult participants (18-64 years, inclusive) and elderly participants (65 to 74 years, inclusive) with MDD with moderate-to-severe anhedonia (ANH+) (MDD ANH+).

Participants will be entering into this study by roll-over following completion of the Double-blind (DB) Treatment Phase of one of the 2 short-term DB efficacy studies (67953964MDD3001 or 67953964MDD3002, hereafter referred to as MDD3001 and MDD3002) of aticaprant as adjunctive treatment for MDD (referred to as "transferred-entry participants"). Transferred-entry participants may participate in this study only if it is clinically appropriate in the opinion of the investigator. If needed, depending on the roll-over enrollment, the sponsor may also open the study for direct recruitment of participants. Therefore, the protocol provides information for direct enrollment of participants (which are referred to as "direct-entry participants"). Of note, this option will not be made available at the start of the study.

BENEFIT-RISK ASSESSMENT

The safety, tolerability, and efficacy of aticaprant has been studied so far in short-term studies (up to 8 weeks). Therefore, the benefit-risk profile of adjunctive aticaprant therapy with longer treatment has not been established. This is the first Phase 3 study investigating the long-term safety and efficacy of aticaprant therapy and specifically, the long-term safety and efficacy of adjunctive aticaprant in participants with MDD. The study will initially enroll participants through roll-over from 2 short-term efficacy studies MDD3001 and MDD3002 (transferred-entry participants). Additionally, participants may be enrolled

directly into the study to meet the target of achieving the required number of participants with 6-month and 1-year exposure to aticaprant.

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

CCI

CCI

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.

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

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

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

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Safety (Primary Objectives)	
To assess the long-term safety and tolerability of aticaprant administered as adjunctive therapy to a current antidepressant (SSRI or SNRI) in all participants with MDD	• AEs, including AEs of special interest (AESI). • Change from baseline in vital signs. • Weight/body mass index (BMI). • Suicidality assessment using the Columbia Suicidality Severity Rating Scale (C-SSRS). • Laboratory parameters. • 12-lead ECG. • Assessment of withdrawal symptoms using the Physician Withdrawal Checklist, 20-item (PWC-20). • Proportion of participants with clinically relevant sexual dysfunction over time in the Arizona Sexual Experiences Scale (ASEX) score.
Efficacy (Secondary Objectives)	
To assess the long-term efficacy of aticaprant administered as adjunctive therapy to an antidepressant (SSRI/SNRI) in adult participants and elderly participants with MDD ANH+ who have had an inadequate response to the current antidepressant therapy on the following:	

Objectives	Endpoints
Depressive symptoms (clinician- and patient-reported)	- Change from baseline over time in the MADRS total score. - Change from baseline over time in the Patient Health Questionnaire, 9-item (PHQ-9) total score.
Anhedonia symptoms (patient-reported)	Change from baseline over time in CCI () total score.
Overall severity of depressive illness (clinician-reported)	Change from baseline over time in the Clinical Global Impression-Severity (CGI-S) total score.
Response rate (clinician-reported)	Proportion of participants with $\geq 50\%$ reduction from baseline in the MADRS total score over time.
Remission of depressive symptoms (clinician-reported)	Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤ 10, over time.

HYPOTHESIS

There is no formal hypothesis for this safety study.

OVERALL DESIGN

This is an open-label (OL), multicenter, long-term study to evaluate the safety and efficacy of aticaprant 10 mg in combination with an oral antidepressant in adult and elderly participants who have MDD and who have had an inadequate response to an SSRI or an SNRI in the current depressive episode. Transferred-entry participants from Studies MDD3001 or MDD3002 will be enrolled in this study. Additionally, participants may be enrolled directly into the study to meet the target of achieving the required number of participants with 6 months and 1 year of exposure to aticaprant.

This study will consist of 3 phases:

- Screening Phase (evaluate eligibility in direct-entry participants only): up to 30 days prior to the first dose administration. Transferred-entry participants will enter directly into the OL Treatment Phase,
- OL Treatment Phase: 52 weeks (both direct- and transferred-entry),
- Follow-up Phase: up to 2 weeks (both direct- and transferred-entry).

If a participant prematurely discontinues study intervention before the end of the OL Treatment Phase (ie, before completing Visit 2.14) for reasons other than withdrawal of consent, an End-of-treatment (EOT)/Early Withdrawal (EW) Visit (ie, Visit 2.14) should be conducted preferably the day after the last dose of study intervention, followed by the Follow-up Phase. If Visit 2.14 is conducted on the same day as a scheduled visit, duplicate assessments are not required. In the case of early discontinuation of the study intervention further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or participant's treating physician, and changes to current antidepressant treatment are permitted. The decision to continue the current oral antidepressant will be at the discretion of the investigator.

The worldwide COVID-19 pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or study participants become potentially exposed to or infected with COVID-19. To assure the safety of study participants, maintain compliance with Good Clinical Practice (GCP), and minimize risks to study integrity, if necessary, in consultation with the sponsor, the method of assessments may be changed (eg, paper assessments replaced by electronic assessments and vice versa). In addition, site visits may be replaced with telephone, internet-based videoconferencing applications, or home visits by qualified health care professionals (HCP). Rating scales/safety assessments can continue to be administered via video teleconferencing (MADRS) or phone (other assessments). Every effort should be made to complete the MADRS assessment via video

teleconferencing and within the scheduled timeframe; if this cannot occur, the sponsor medical monitor or delegate should be contacted for direction. Normal procedures, as detailed in this protocol, will be resumed as soon as possible thereafter. For participants who receive an approved or authorized vaccine, it is recommended that this occurs at least 5 days prior to the start of dosing.

Screening Phase

This 4-week Screening Phase is only for direct-entry participants. Transferred-entry participants from Studies MDD3001 or MDD3002 will not participate in this phase.

The direct-entry participants will need to meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for recurrent or single episode MDD, without psychotic features, based upon clinical assessment and confirmed by the Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials Version (SCID-CT). Participants ≥ 65 years of age must have had the first onset of depression prior to 55 years of age. Eligible participants must have a 17-item Hamilton Depression Rating Scale (HDRS-17) total score ≥ 20 at the first and second screening interviews with no greater than 20% improvement from the first to second independent HDRS-17 assessments at screening.

Moreover, all direct-entry participants must have had an inadequate response to at least 1 oral antidepressant treatment (SSRI or SNRI), administered at an adequate dose (at or above the minimum therapeutic dose per the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire [MGH ATRQ]) and duration (at least 6 weeks) in the current episode of depression. An inadequate response is defined as $<50\%$ reduction in depressive symptom severity but with some improvement ($>0\%$) (ie, there may be minimal to moderate symptomatic improvement since the initiation of treatment, but some of the initial symptoms are still present, troubling to the participant and affecting behavior and function) as assessed by the MGH ATRQ. The inadequate response must include the participant's current SSRI/SNRI treatment. To characterize the presence and severity of anhedonia from the patient perspective, Snaith-Hamilton Pleasure Scale (SHAPS) assessment of hedonic capacity will be collected at screening for direct-entry participants. A Site Independent Qualification Assessment (SIQA) will assess the validity of the participants' diagnosis and antidepressant treatment response for inclusion in the study.

Participants meeting all of the inclusion and none of the exclusion criteria are eligible to proceed to the OL Treatment Phase.

Open-label Treatment Phase

Both transferred-entry and direct-entry participants will participate in this 52-week OL Treatment Phase.

For transferred-entry participants, results of all assessments performed on Day 43 of the DB Treatment Phase of the parent study (Visit 2.7 of Studies MDD3001 or MDD3002) will not be repeated as part of this study. For these participants, the Day 43 visit of the parent study will coincide with Day 1 (OL Baseline, Visit 2.1) for the current study. There is no gap foreseen between the studies.

All eligible participants (transferred- and direct-entry) will receive OL aticaprant treatment at a dosage of 10 mg/day starting on Day 1 (OL Baseline) without breaking the blind from the prior study for the transferred-entry participants.

Aticaprant will be self-administered by participant at home daily at the same time preferably in the morning. The first dose will be taken on Day 1 on-site after pre-dose procedures and will be witnessed by the investigator or a responsible designee. Participants will receive instructions on compliance with the study intervention treatment. Study site personnel will instruct participants on how to store and take the OL aticaprant supplied during this study for at home use. 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. Participants will be provided with a paper diary to capture study intervention use.

All participants should continue to take their current SSRI/SNRI antidepressant throughout the entire study (see Section 6.8.1 for a list of antidepressants), unless significant tolerability issue occurs, in which case the oral SSRI/SNRI antidepressant may be discontinued and if appropriate, switched to a new SSRI/SNRI antidepressant (from those listed in Section 6.8.1). The proposed change and the reason must be discussed with the study responsible physician/scientist or designee and documented in the electronic case report form (eCRF).

Safety and efficacy assessments, biomarkers sampling, and other study procedures will be performed per the Schedule of Activities (SoA). If a participant withdraws from study intervention, an EOT/EW Visit per the SoA will be performed as soon as possible, preferably the day after the last dose of aticaprant.

End-of-treatment Visit

All participants will have an EOT Visit, preferably the day after the last dose of study intervention (aticaprant). After completion of this visit, the participant enters the Follow-up Phase. Entry to the Follow-up Phase should not be conducted in participants who withdraw consent from study assessments; however, they should complete the OL EOT Visit if they are willing to do so.

Follow-up Visit

Participants will return to the study site for a Follow-up Visit within 7 to 14 days after Visit 2.14 (EOT/EW). At the Follow-up Visit, safety and efficacy assessments/procedures will be completed per the SoA.

At the start of the Follow-up Phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician.

No study intervention will be administered during this phase.

NUMBER OF PARTICIPANTS

The study will initially enroll participants (MDD with and without moderate-to-severe anhedonia, MDD ANH+ and MDD ANH-) through roll-over from 2 short-term efficacy studies: MDD3001 and MDD3002 (transferred-entry participants). Transferred-entry participants who complete the 6-week DB Treatment Phase in either of the short-term studies (regardless of their treatment response) may participate in this study if this is clinically appropriate in the opinion of the investigator if they meet the specific eligibility criteria for transferred-entry participants. Efforts will be made to ensure good representation in terms of race, gender and ethnicity.

Based on the targeted enrollment in the 2 short-term efficacy studies it is anticipated that approximately 840 participants from these studies will participate in the long-term safety study. Additionally, participants may be enrolled directly into the study to meet the target of achieving the required number of participants with 6 months and 1 year of exposure to aticaprant. Direct enrollment allows sites to enroll directly into the study at some point during the study if additional number of participants are needed to support enrollment. The sponsor will notify the study sites when direct enrollment might be open.

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

INTERVENTION GROUPS AND DURATION

The study intervention (aticaprant) will be self-administered by the participant at home once daily, preferably in the morning and around the same time during the OL Treatment Phase. The maximum duration of participation in the study for an individual participant (including screening [if applicable], OL

Treatment, and Follow-up Phases) will be up to 54 weeks for transferred-entry participants or up to 58 weeks for direct-entry participants.

SAFETY EVALUATIONS

Safety evaluations during the OL Treatment Phase will include collection of treatment-emergent AEs, including AESI and concomitant medications, as well as assessment with physical examination, body weight measurements, vital signs, 12-lead ECG, urine drug test, alcohol breath test, and clinical laboratory tests (hematology, serum chemistry panel, lipid panel, hemoglobin A1c [HbA1c], thyroid-stimulating hormone [TSH], free thyroxine [FT₄], and urinalysis). Serum or urine pregnancy tests will be performed for female participants of childbearing potential. Additional serum and urine pregnancy tests and drug and alcohol tests may be conducted as needed per the investigator's judgment. Menstrual cycles will be tracked during the study in premenopausal female participants who are still having their menses, using a participant diary and participant's verbal report. In addition, emergence of suicidal ideation will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), cognitive impairment will be assessed using the Mini Mental State Examination (MMSE) at screening only (participants 65 to 74 years of age, inclusive), potential withdrawal symptoms will be assessed by the clinician using the PWC-20, and sexual functioning will be assessed using the Arizona Sexual Experiences Scale (ASEX).

EFFICACY EVALUATIONS

The following efficacy evaluations will be summarized descriptively at each scheduled visit using observed data using the following: Depression symptoms using the MADRS as well as a patient-reported outcome scale (PHQ-9); anhedonia symptoms using CCI and CCI

and CCI global change in severity (CGI-S); CCI measurement of anhedonia (SHAPS); CCI

The proportion of participants who responded or remitted based on the MADRS total score will be provided over time.

STATISTICAL METHODS

Sample Size Calculation

No formal sample size calculation was performed for the study. Based on the targeted enrollment in the 2 short-term efficacy studies, it is anticipated that approximately 715 participants enrolled in the rest of the world (ROW) (ie, countries/territories other than China and Japan [if participating]) from these studies will participate in this long-term safety study. Assuming that 50% of the participants will complete 6 months and 33% will complete 12 months of aticaprant exposure, this sample size will meet the International Council on Harmonisation (ICH) E1 guidance requirement of achieving at least 300 participants who have received treatment with aticaprant for 6 months and at least 100 participants for 12 months. Additionally, it is anticipated that approximately 80 participants from China will participate in the study. In the event Japan participates in the study, approximately 45 participants will be enrolled in this country/territory. Therefore, a total of approximately 840 participants is expected to roll over from the short-term efficacy studies. Additionally, participants may be enrolled directly into the study to meet the target of achieving the required number of participants with 6 months and 1 year of exposure to aticaprant.

Statistical Analysis

The analysis of safety and efficacy data will be performed on the full analysis set (FAS) which includes all participants who took at least 1 dose of study intervention. The elderly participants will be summarized separately for selected safety and efficacy analyses.

The data will be presented by treatment sequence, namely: placebo/aticaprant 10 mg, aticaprant 10 mg/aticaprant 10 mg for transferred-entry participants (depending on the study intervention group in the short-term efficacy studies), and no DB/aticaprant 10 mg for direct-entry participants. Additionally, a total aticaprant group will be presented.

Two baselines are defined for this study. Baseline (DB/OL) is defined as the last assessment taken on or prior to the first dose of study intervention including the short-term studies for transfer-entry participants. Baseline (OL) is defined as the assessment taken on or prior to the first dose of study intervention in the OL study.

Safety Analyses

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

Descriptive statistics of body weight, temperature, pulse/heart rate, respiratory rate, pulse oximetry and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point by treatment sequence. Changes in body weight and BMI will be summarized descriptively.

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

The effects on ECG measurements (heart rate, PR interval, QT interval, and QTc interval) will be evaluated using descriptive statistics and frequency tabulations. QTc intervals will be calculated using the Bazett and Fridericia correction methods, and descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point by treatment sequence. 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.

Results from the ASEX, C-SSRS and PWC-20 will be summarized by treatment sequence.

Efficacy Analyses

Depression symptoms using the MADRS as well as a patient-reported outcome (PHQ-9), anhedonia symptoms using CCI CCI

global change in severity (CGI-S) as well as CCI

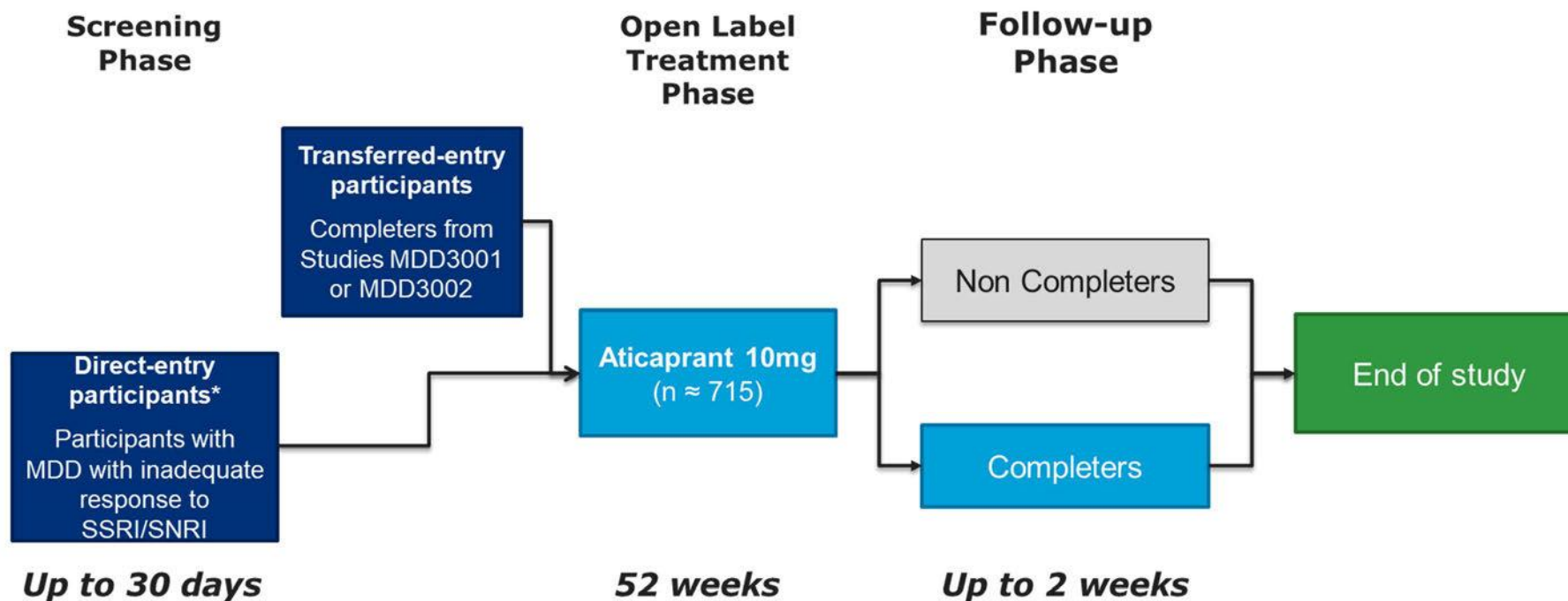
will be summarized descriptively at each scheduled visit by treatment sequence using observed data. The proportion of participants who responded and remitted based on the MADRS total score will be provided over time.

Interim Analysis

An interim lock of the database is planned once 300 participants have been exposed to aticaprant for 6 months and 100 participants for 1 year in study sites from countries/territories other than China and Japan (if participating) in order to support filing in the ROW. If necessary, other interim lock(s) may be implemented once all the participants in China or Japan (if participating) have completed at least 6 months of study participation depending on the requirement by the respective health authorities.

1.2. Schema

Figure 1: Schematic Overview of the Study



* Screening Phase applies only to direct-entry participants. Direct-entry option will not be available from the start of the study and the main enrollment will be from the roll-over from MDD3001 and MDD3002.

All participants should continue to take their SSRI or SNRI antidepressant therapy at an adequate dose (at or above the minimum therapeutic dose per MGH ATRQ) throughout the study (see Section 6.8.1 for further details).

Additionally, it is anticipated that approximately 80 participants from China will participate in the study. In the event Japan participates in the study, approximately 54 participants will be enrolled in this country/territory.

MDD=major depressive disorder; MDD3001=67953964MDD3001; MDD3002=67953964MDD3002; MGH ATRQ=Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

1.3. Schedule of Activities (SoA)

Phase	Screening ^a (direct-entry participants only)		Open-label Baseline ^b	OL Treatment Phase				Follow-up (all participants)
				Every 4-week visits	Only every 12-week visits	Unscheduled ^c	EOT/EW ^d	
Visit Number	1.1	1.2	2.1 ^b	2.2, 2.3, 2.5, 2.6, 2.8, 2.9, 2.11, 2.12	2.4, 2.7, 2.10, 2.13		2.14	3.1
Study Days	-30 to -2							
Study Week			1 (Day 1)	4, 8, 16, 20, 28, 32, 40, 44	12, 24, 36, 48		52	7-14 days after Visit 2.14 (EOT/EW)
Visit window (days)				±7	±7		+7	
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	C	C	C	C	C
Study Procedure								
Screening/Administrative for Direct-entry Participants								
Informed consent (ICF) ^e	X							
ICF for optional genetic research samples ^e	X							
ICF for optional substudies ^e	X							
Inclusion/exclusion criteria	X		X ^y					
Height	X							
Weight	X		X		X		X	X
Menstrual cycle tracking ^f	X		X	X	X		X	
HDRS-17 Independent Remote Rater (via audio conferencing)	X	X						
SCID-CT	X							
MGH ATRQ	X							
Site Independent Qualification Assessment (for direct-entry participants only)	X							
Mini Mental State Examination	X ^t							
Pre-study therapy	X							

Phase	Screening ^a (direct-entry participants only)		Open-label Baseline ^b	OL Treatment Phase				Follow-up (all participants)
				Every 4-week visits	Only every 12-week visits	Unscheduled ^c	EOT/EW ^d	
Visit Number	1.1	1.2	2.1 ^b	2.2, 2.3, 2.5, 2.6, 2.8, 2.9, 2.11, 2.12	2.4, 2.7, 2.10, 2.13		2.14	3.1
Study Days	-30 to -2							
Study Week			1 (Day 1)	4, 8, 16, 20, 28, 32, 40, 44	12, 24, 36, 48		52	7-14 days after Visit 2.14 (EOT/EW)
Visit window (days)				±7	±7		+7	
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	C	C	C	C	C
Study Procedure								
Medical History, psychiatric history, and demographics	X							
Employment status	X						X	
Preplanned surgery/procedure(s)	X							
Evaluation of SSRI/SNRI antidepressant compliance ^g	X		X ^y		X (only Week 24)		X	
Screening/Administrative for Transferred-entry Participants								
Informed consent (ICF) ^u			X					
ICF for optional genetic research samples ^u			X					
ICF for optional substudies ^u			X					
Inclusion/exclusion criteria			X					
Weight			X		X		X	X
Menstrual cycle tracking ^f			X	X	X		X	
Preplanned surgery/procedure(s)			X					
Evaluation of SSRI/SNRI antidepressant compliance ^g			X ^y		X (only Week 24)		X	

Phase	Screening ^a (direct-entry participants only)		Open-label Baseline ^b	OL Treatment Phase				Follow-up (all participants)
				Every 4-week visits	Only every 12-week visits	Unscheduled ^c	EOT/EW ^d	
Visit Number	1.1	1.2	2.1 ^b	2.2, 2.3, 2.5, 2.6, 2.8, 2.9, 2.11, 2.12	2.4, 2.7, 2.10, 2.13		2.14	3.1
Study Days	-30 to -2							
Study Week			1 (Day 1)	4, 8, 16, 20, 28, 32, 40, 44	12, 24, 36, 48		52	7-14 days after Visit 2.14 (EOT/EW)
Visit window (days)				±7	±7		+7	
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	C	C	C	C	C
Study Procedure								
Study Intervention Administration								
Dispense aticaprant ⁱ			X	X	X			
Dispense and/or review paper medication diary ^h			X	X	X		X	
Aticaprant accountability			X	X	X	X	X	
Safety Assessments								
Physical examination	X		X ^y				X	
12-lead ECG ^{q,w}	X		X ^y		X		X	
Vital signs	X	X	X ^y	X	X	X	X	X
Urine drug test	X		X ^y	X (only Weeks 4 & 8)	X	X	X	
Alcohol breath test	X		X ^y		X			
Serum/Urine pregnancy test ^{j,1}	X ^k		X ^y	X	X	X	X	
C-SSRS: Screening/Baseline version	X							
C-SSRS: Since last visit version		X	X ^y	X	X	X	X	X
ASEX			X		X		X	
PWC-20							X	X

Phase	Screening ^a (direct-entry participants only)		Open-label Baseline ^b	OL Treatment Phase				Follow-up (all participants)
				Every 4-week visits	Only every 12-week visits	Unscheduled ^c	EOT/EW ^d	
Visit Number	1.1	1.2	2.1 ^b	2.2, 2.3, 2.5, 2.6, 2.8, 2.9, 2.11, 2.12	2.4, 2.7, 2.10, 2.13		2.14	3.1
Study Days	-30 to -2							
Study Week			1 (Day 1)	4, 8, 16, 20, 28, 32, 40, 44	12, 24, 36, 48		52	7-14 days after Visit 2.14 (EOT/EW)
Visit window (days)				±7	±7		+7	
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	C	C	C	C	C
Study Procedure								
Efficacy Assessments^e								
MADRS (SIGMA version) (site rater via videoconference)			X ^y	X	X	X	X	X
SHAPS	X		X ^y	X	X	X	X	X
CCI			X	X	X	X	X	X
CGI-S (depression)			X ^y	X	X	X	X	X
CCI			X	X	X	X	X	X
PHQ-9			X		X	X	X	X
CCI			X	X	X	X	X	X
CCI			X		X		X	X
CCI			X		X		X	
CCI			X		X		X	X
CCI			X		X		X	
CCI (only direct-entry participants and those transferred from MDD3001)			X		X		X	
CCI (only direct-entry participants and those transferred from MDD3001)			X		X (only Week 24)		X	

Phase	Screening ^a (direct-entry participants only)			OL Treatment Phase				Follow-up (all participants)
			Open-label Baseline ^b	Every 4-week visits	Only every 12-week visits	Unscheduled ^c	EOT/EW ^d	FU Visit
Visit Number	1.1	1.2	2.1 ^b	2.2, 2.3, 2.5, 2.6, 2.8, 2.9, 2.11, 2.12	2.4, 2.7, 2.10, 2.13		2.14	3.1
Study Days	-30 to -2							
Study Week			1 (Day 1)	4, 8, 16, 20, 28, 32, 40, 44	12, 24, 36, 48		52	7-14 days after Visit 2.14 (EOT/EW)
Visit window (days)				±7	±7		+7	
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	C	C	C	C	C
Study Procedure								
Clinical Laboratory Tests								
Hematology, chemistry	X		X		X		X	
Lipid panel (fasting)		X						
Urinalysis	X		X ^y		X		X	
TSH/FT ₄ ; HbA1c	X							
Biomarkers Assessments								
Morning blood sample collection ^m			X ^y		X (only Week 24)		X	
Pharmacogenomics (RNA) Assessments ^x								
Morning blood sample collection ⁿ			X ^y				X	
Digital Health								
CCI [REDACTED]		X	X		X (only Week 24)		X	
CCI [REDACTED] (optional) ^{o,p}	← Continuous →							
Ongoing Participant Review								
Diary for current antidepressant compliance (Dispense/Review)	X		X ^y	X	X	X	X	
Concomitant therapy	← Continuous →							

Phase	Screening ^a (direct-entry participants only)		Open-label Baseline ^b	OL Treatment Phase				Follow-up (all participants)
				Every 4-week visits	Only every 12-week visits	Unscheduled ^c	EOT/EW ^d	
Visit Number	1.1	1.2	2.1 ^b	2.2, 2.3, 2.5, 2.6, 2.8, 2.9, 2.11, 2.12	2.4, 2.7, 2.10, 2.13		2.14	3.1
Study Days	-30 to -2							
Study Week			1 (Day 1)	4, 8, 16, 20, 28, 32, 40, 44	12, 24, 36, 48		52	7-14 days after Visit 2.14 (EOT/EW)
Visit window (days)				±7	±7		+7	
Clinic Visit (C) or Remote Contact (RC)	C	C or RC	C	C	C	C	C	C
Study Procedure								
Adverse events								

Abbreviations: ASEX=Arizona Sexual Experiences Scale; C=clinic visit; CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia Suicide Severity Rating Scale; CCI ECG=electrocardiogram; EOT=End-of-treatment; CCI EW=Early Withdrawal; FT₄=free thyroxine; FU=Follow-up; CCI HbA1c=hemoglobin A1c / glycated hemoglobin; HDRS-17=17-item Hamilton Depression Rating Scale; ICF=informed consent form; MADRS=Montgomery-Åsberg Depression Rating Scale; MDD3001=67953964MDD3001; MGH ATRQ=Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; MMSE=Mini Mental State Examination; OL=Open-label; PRO=patient-reported outcome; CCI ; PHQ-9=Patient Health Questionnaire, 9-item; CCI PWC-20=Physician Withdrawal Checklist, 20-item; CCI RC=remote contact; SCID-CT=Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version; SHAPS=Snaith-Hamilton Pleasure Scale; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TSH=thyroid-stimulating hormone; CCI

Note: During the site visits it is recommended that procedures should be performed in the following sequence: Blood and urine collection (when in fasted condition), dosing, breakfast, PRO, interview with site-based rater (MADRS [SIGMA version] via videoconference, if not completed before the actual visit, CGI-S), C-SSRS, and safety assessments.

Footnotes:

- a. Screening assessments are for direct-entry participants only. Screening period extension up to 3 weeks may be considered, if needed, after consultation with sponsor medical monitor.
- b. Results for all assessments performed on Day 43 of Study MDD3001 or MDD3002 (transferred-entry participants) will not be repeated as part of Visit 2.1. For transferred-entry participants, the Day 43 visit of the Double-blind Treatment Phase in the parent study will coincide with OL Baseline (Visit 2.1) for this study. No gap between studies is foreseen. All transferred-entry participants must meet all of transferred-entry participant-specific inclusion criteria and none of exclusion criteria in order to be enrolled.
- c. An investigator may choose to perform an unscheduled visit at any time during the study due to efficacy, safety, or tolerability concerns. The procedures listed are the minimum to be performed during any unscheduled visit during the treatment phase of the study. Additional tests and assessments may be done at the investigator's discretion. Scheduled visits should continue after the unscheduled visit based on Day 1.
- d. If a participant discontinues study intervention before the end of study, an EOT/EW Visit (ie, Visit 2.14) assessments should be conducted preferably the day after the last dose of study intervention, or as soon as the participant is able to return to the clinic site. Follow-up assessments should be obtained 7-14 days after the EOT/EW Visit. Participants who withdraw their consent should not participate in the FU Visit but should, if willing, complete the EOT/EW Visit.
- e. The ICF must be signed before first study-related activity. Each rescreened participant will be assigned a new participant number, will need to sign a new ICF and restart a new Screening Phase.
- f. Start date (first day) of last menstrual period and length of menstrual cycle (days) will be collected from premenopausal female participants who are still having their menses.
- g. During the screening phase (direct-entry participants only), compliance to the current antidepressant treatment must be confirmed by documented records (eg, medical/pharmacy/prescription record, a letter from a treating physician, etc). During the OL Treatment Phase, the compliance to the ongoing 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.
- h. Dispense the study intervention paper diary at Visit 2.1 and review it at all clinical visits.
- i. Study intervention will be supplied every 4 weeks +/-7 days.
- j. Applicable to female participants of childbearing potential. Additional serum and urine pregnancy tests may be performed as determined necessary by the investigator, to establish the absence of pregnancy at any time during the participant's participation in the study.
- k. Serum pregnancy test at screening is required for direct-entry participants only.
- l. Only female participants of childbearing potential who are entering directly this study must have a negative serum pregnancy test at screening and a negative urine pregnancy test before treatment starts.
- m. Biomarker samples will be collected in the morning under fasting conditions.
- n. Blood samples will be collected only from participants who have consented to provide optional RNA samples for research.
- o. Participants who opted for this assessment in the MDD3001 study may continue completing this assessment in this study upon providing consent.
- p. The CCI assessments performed using the smartphone applications are optional and will only be performed on a subset of participants with a dedicated personal smartphone. The smartphone application data collection will run continuously in the background once set up is established at screening for participants who have opted for this.
- q. Twelve-lead ECG readings will be performed pre-dose. During Screening or at Visit 2.1 (Day 1), if QTcF is prolonged based on site evaluated ECG, a total of three 12-lead ECGs should be obtained at least 4 minutes apart. The average QTcF of the three 12-lead ECGs will then be used to determine participant's eligibility. During the OL Treatment Phase, if a clinically significant finding is identified in QTcF, the average QTcF of 3 ECGs, recorded 4 minutes apart, will be used to assess QTc stopping criteria.
- r. The CCI will only be performed in a subset of English-speaking countries/territories.
- s. All PRO assessments should be conducted in the order listed in the above SoA table. Participant-reported outcome assessments should be administered before all

other study related procedures during a clinic visit. The following PRO assessments will be collected electronically in a 7-day window prior to the clinic visit:

CCI [REDACTED] If a participant does not complete the PRO assessments ahead of the clinic visit, the PROs will be collected at the clinic visit.

- t. The MMSE screening assessment is to be performed only in participants 65 to 74 years of age, inclusive.
- u. The ICF must be signed before first study-related activity (see Section 4.1.3).
- v. For participants that require translation of the CCI [REDACTED] into their local language, the collection of the CCI [REDACTED] is optional until the final, approved translation is available.
- w. If blood sampling or vital sign measurement is scheduled for the same time point as 12-lead ECG recording, the procedures are recommended to be performed in the following order: 12-lead ECG, vital signs, blood draw.
- x. Not applicable for China.
- y. Study procedure or assessment must be performed before dosing.

2. INTRODUCTION

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

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

Aticaprant has shown antidepressant-like effects in preclinical studies and had synergistic effects when administered with a subactive dose of imipramine. Clinical data from multiple Phase 1 and results from 2 well controlled Phase 2 studies provide complimentary positive evidence for efficacy of aticaprant in patients with major depression with anhedonia (Krystal 2020). Study 67953964MDD2001 provides proof of efficacy showing that after 6 weeks of treatment MDD participants randomized to aticaprant added to ongoing antidepressant achieved statistically significant and clinically meaningful reduction in overall depression severity on the Montgomery-Åsberg Depression Rating Scale (MADRS, primary endpoint) compared with those who continued on the current antidepressant plus placebo. CCI

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

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

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

2.1. Study Rationale

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

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

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

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

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

The proposed study, 67953964MDD3003 (hereafter referred to as MDD3003), is an open-label (OL), multicenter, long-term study to evaluate the safety and efficacy of aticaprant in combination with an oral antidepressant in adult participants (18-64 years, inclusive) and elderly participants (65-74 years, inclusive) who have MDD and who have had an inadequate response to an SSRI or an SNRI in the current depressive episode.

In contrast with available data about short-term antidepressant effects and safety and tolerability of aticaprant up to 6 weeks of exposure, the safety and efficacy of its long-term administration has not been assessed systematically. Therefore, this study will address the long-term safety and efficacy of aticaprant. In accordance with International Council for Harmonisation (ICH) E1 guidance, this study will aim to collect safety exposure to aticaprant for at least 300 participants for 6 months and at least 100 participants for a year.

2.2. Background

2.2.1. Nonclinical Studies

2.2.1.1. Nonclinical Pharmacology

Kappa Opioid Receptor Studies: Aticaprant (JNJ-67953964) is a potent, high-affinity antagonist (inhibition constant $[K_i]=0.807$ nM) for KORs, with demonstrated selectivity over MORs and DORs, as assessed by in vitro binding and functional assays. CCI

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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

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2.2.1.2. Safety Pharmacology

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2.2.1.3. 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).

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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.

2.2.1.4. Pharmacokinetic Profile in Animals

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

[REDACTED]

2.2.2. Clinical Studies

2.2.2.1. Human Pharmacokinetics

Single-dose administration (Study I2Z-MC-LAFA [[Lowe 2014](#)]) of aticaprant as an oral capsule to healthy participants resulted in rapid absorption with peak plasma concentrations typically occurring at 1.5 to 4 hours post-dose, proportional increases in exposure with increasing dose (ranging from 2 to 60 mg), and a concentration-time profile indicative of biexponential disposition. After the 10-mg dose, the geometric mean (present of coefficient of variation percentage [CV%]) for apparent plasma clearance was 28.7 L/hr (36%), apparent volume of distribution at steady state was 1,160 L (25%), and half-life ($t_{1/2}$) was 38.5 hours (22%). The mean $t_{1/2}$ of aticaprant ranged from 21.3 to 38.5 hours and appeared to be independent of dose in the single ascending dose study.

Administration of multiple doses of aticaprant 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.

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2.2.2.2. Efficacy Studies

A completed Phase 2a investigator-initiated study (IIS) (FAST-MAS) designed to determine whether KOR antagonism could have effects supportive of therapeutic benefit for anhedonia in patients with mood-anxiety spectrum disorders and anhedonia, revealed a significant Group×Time interaction in reward gain anticipation ($p=0.019$) (a priori primary outcome) and loss anticipation ($p<0.001$). In this study, participants with self-reported anhedonia (with a mood or anxiety disorder) were administered monotherapy for a period of 8 weeks: 10-mg aticaprant ($n=43$) 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

(Krystal 2020; Pizzagalli 2020).

The Phase 2 Study 67953964MDD2001 was a randomized, DB, placebo-controlled, parallel-group, multicenter study investigating the efficacy, safety, tolerability, and PK of adjunctive aticaprant in participants with MDD. The objective of this study was to evaluate the efficacy of 10-mg daily aticaprant versus placebo when administered as an adjunctive treatment to participants with MDD who had partially responded to standard-of-care treatment with SSRI/SNRIs. The primary endpoint was reduction of symptoms of depression, as assessed by the change from baseline on the MADRS during a 6-week treatment period. CCI

The Phase 2 study 67953964MDD2001 showed greater reduction in overall depression severity on the MADRS in participants with MDD treated with aticaprant added to ongoing antidepressant with partial response, compared with those who continued treatment with just their current

antidepressant plus placebo. Participants randomized to aticaprant had a significantly greater reduction in depression severity on the MADRS during the 6-week treatment period with MADRS (LS) mean difference change from baseline at Treatment Week 6 between aticaprant and placebo being -2.1 with 80% 1-sided CI upper limit of -1.09 (1-sided $p=0.044$) in the eITT population. In the fITT population, the estimated LS mean difference was of a larger magnitude -3.1 with 80% 1-sided CI upper limit of -2.21; 1-sided $p=0.002$. CCI

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2.2.2.3. Safety Studies

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

Safety results from Study 67953964MDD2001 in participants with MDD were consistent with the known safety profile of the drug over a 6-week exposure period. Overall, during the treatment period, 47.1% of participants receiving aticaprant experienced a treatment-emergent adverse event (TEAE), compared with 35.7% of participants receiving placebo. The most common TEAEs during the treatment phase were (aticaprant vs placebo) headache (11.8% vs 7.1% in the placebo group) and diarrhea (8.2% vs 2.4% in the placebo group). TEAEs of special interest in the aticaprant group that were commonly reported were CCI and CCI (5.9% in the aticaprant group vs 0.0% in placebo).

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

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2.3. Benefit-Risk Assessment

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

2.3.1. Benefits for Study Participation

There is evidence to suggest that with its targeted mechanism of action the selective KOR antagonism may result in improvement of symptoms of depression linked to impaired functioning in the reward circuitry (like anhedonia and amotivation) ([Borsini 2020](#)) and which are poorly addressed by the current standard-of-care SSRIs/SNRIs, ([Calabrese 2014](#); [Craske 2019](#); [Vriezeet 2013](#)). Presence and persistence of symptoms like elevated anhedonia predict poor outcome and chronic course of the disease ([Moos 1999](#); [Spijker, 2001](#); [Uher 2012](#)). Available data from nonclinical and clinical studies (Phase 1 and Phase 2 studies) with aticaprant support the scientific and clinical rationale for the use of selective KOR antagonists in the treatment of depression with moderate-to-severe anhedonia. Data from the Phase 2 study 67953964MDD2001 showed greater reduction in overall depression severity on the MADRS in participants with MDD treated with aticaprant added to ongoing antidepressant with inadequate response, compared with those who continued on just their current antidepressant plus placebo. The magnitude of the overall antidepressant efficacy was different when examined based on the presence and severity of anhedonia defined using an established self-reported assessment (SHAPS) for severity of anhedonia. CCI

In a post hoc item-level analysis of the MADRS scale, the subgroup of participants with a high level of anhedonia when treated with aticaprant showed overall better effect on symptoms of dysphoria like apparent and reported sadness compared with participants with a low level of anhedonia, and there was improvement in items that reflect the positive affect, namely the anhedonia-specific item inability to feel, and several other items like pessimistic thoughts, lassitude and concentration difficulties which are related to the hedonic capacity as they reflect on individual's interest, engagement, motivation, and activity. Improvement in MADRS scores of symptoms of depression (eg, sadness, tension, appetite, insomnia, and fatigue) were observed. Furthermore, aticaprant was generally safe and well tolerated. Participants in this up to 1-year study will help with evaluating safety of the long-term use of aticaprant. Additionally, the study will provide information on the long-term efficacy of aticaprant as adjunctive therapy to an antidepressant (SSRI/SNRI) in participants with MDD with moderate-to-severe anhedonia (ANH+) and without moderate-to-severe anhedonia (ANH-).

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

2.3.2. Benefit-Risk Assessment for Study Participation

The safety, tolerability, and efficacy of aticaprant has been studied so far in short-term studies (up to 8 weeks). Therefore, the benefit-risk profile of adjunctive aticaprant therapy with longer treatment has not been established. This is the first Phase 3 study investigating the long-term safety and efficacy of aticaprant therapy and specifically, the long-term safety and efficacy of adjunctive aticaprant in participants with MDD. The study will initially enroll participants through roll-over from 2 short-term efficacy studies 67953964MDD3001 and 67953964MDD3002 (hereafter referred to as MDD3001 and MDD3002) (transferred-entry participants). Additionally, participants may be enrolled directly into the study (direct-entry participants) to meet the target of achieving the required number of participants with 6-month and 1-year exposure to aticaprant.

Aticaprant was generally well tolerated in healthy participants after single dose administration up to 60 mg or after multiple-dose administration up to 35 mg for 14 days, with no clinically significant AEs, vital sign measurements, 12-lead ECGs, or clinical laboratory evaluations reported (see Section 2.2.2).

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Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with aticaprant are justified by the anticipated benefits that may be

afforded to participants; this supports further clinical investigation of adjunctive treatment with aticaprant for MDD in patients with moderate-to-severe anhedonia.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Safety (Primary Objectives)	
To assess the long-term safety and tolerability of aticaprant administered as adjunctive therapy to a current antidepressant (SSRI or SNRI) in all participants with MDD	• AEs, including AEs of special interest (AESI). • Change from baseline in vital signs. • Weight/body mass index (BMI). • Suicidality assessment using the Columbia Suicidality Severity Rating Scale (C-SSRS). • Laboratory parameters. • 12-lead ECG. • Assessment of withdrawal symptoms using the Physician Withdrawal Checklist, 20-item (PWC-20). • Proportion of participants with clinically relevant sexual dysfunction over time in the Arizona Sexual Experiences Scale (ASEX) score.
Efficacy (Secondary Objectives)	
To assess the long-term efficacy of aticaprant administered as adjunctive therapy to an antidepressant (SSRI/SNRI) in adult participants and elderly participants with MDD ANH+ who have had an inadequate response to the current antidepressant therapy on the following:	
• Depressive symptoms (clinician- and patient-reported)	• Change from baseline over time in the MADRS total score. • Change from baseline over time in the PHQ-9 total score.
• Anhedonia symptoms (patient-reported)	• Change from baseline over time in CCI () total score.
• Overall severity of depressive illness (clinician-reported)	• Change from baseline over time in the Clinical Global Impression-Severity (CGI-S) total score.
• Response rate (clinician-reported)	• Proportion of participants with $\geq 50\%$ reduction from baseline in the MADRS total score over time.
• Remission of depressive symptoms (clinician-reported)	• Proportion of participants with remission of depressive symptoms, defined as a MADRS total score ≤ 10, over time.
Exploratory	
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Objectives	Endpoints
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Digital Biomarkers	
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HYPOTHESIS

There is no formal hypothesis for this safety study.

4. STUDY DESIGN

4.1. Overall Design

This is an OL, multicenter, long-term study to evaluate the safety and efficacy of aticaprant 10 mg in combination with an oral antidepressant in adult and elderly participants with MDD who have had an inadequate response to an SSRI or SNRI in the current depressive episode. Participants will enter the study either directly (referred to as "direct-entry participants") or after completing the double-blind (DB) phase of short-term efficacy studies of aticaprant as adjunctive treatment for MDD (Studies MDD3001 or MDD3002); these participants are referred to as "transferred-entry participants."

This study will consist of 3 phases ([Figure 1](#)):

- Screening Phase (up to 30 days): this phase is only for direct-entry participants
- OL Treatment Phase: up to 52 weeks (all participants, ie, direct- and transferred-entry); and
- Follow-up Phase: up to 2 weeks (all participants, ie, direct- and transferred-entry)

In the case of early discontinuation of the study intervention further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or participant's treating physician, and changes to current antidepressant treatment are permitted. The decision to continue the current oral antidepressant will be at the discretion of the investigator.

The maximum duration of participation in the study for an individual participant (including screening [if applicable], OL Treatment, and Follow-up Phases) will be up to 54 weeks for transferred-entry participants or up to 58 weeks for direct-entry participants.

4.1.1. Study Intervention(s)

All eligible participants will receive OL aticaprant treatment at a dose of 10 mg starting on Day 1 (OL Baseline). Transferred-entry participants (ie, from the DB short-term studies MDD3001 and MDD3002) will not be unblinded before commencement of OL aticaprant treatment; their treatment assignment in the short-term study will remain blinded until the database lock of the short-term study.

All participants should continue to take their OL current SSRI/SNRI antidepressant throughout the entire study treatment phase (see [Section 6.8.1](#) for a list of antidepressants), unless a significant tolerability issue occurs, in which case the oral SSRI/SNRI antidepressant may be discontinued and switched to a new SSRI/SNRI antidepressant (from those listed in [Section 4.1.3](#)). The proposed change and the reason must be discussed with sponsor's study responsible physician/scientist or designee and documented in the eCRF.

4.1.2. Screening Phase

This 4-week Screening Phase is only for direct-entry participants. Transferred-entry participants from Studies MDD3001 or MDD3002 will not participate in this phase of the study.

For direct-entry participants, after providing signed informed consent, all the participants experiencing a major depressive episode will be screened to evaluate their eligibility for study participation. Participants must meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for recurrent or single episode MDD, without psychotic features, based upon clinical assessment and confirmed by the Structured Clinical Interview for DSM-5 Axis I Disorders - Clinical Trials Version (SCID-CT). Participants 65 years of age or older must have had the first onset of depression prior to 55 years of age.

At the start of screening participants must have had an inadequate response to at least 1 oral antidepressant treatment (SSRI or SNRI), administered at an adequate dose (at or above the minimum therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current episode of depression (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 but with some improvement (>0%) (ie, there may be minimal to moderate symptomatic improvement since the initiation of treatment, but some of the initial symptoms are still present, troubling to the participant and affecting behavior and function) as assessed by the MGH ATRQ. This must apply to the participant's current antidepressant treatment. Medical/pharmacy/prescription records or records of conversation with the treating physician, or other equivalent documents can be used to verify the adequacy of the current antidepressant trial.

To characterize the presence and severity of anhedonia from the participant perspective, SHAPS will be collected at screening and at baseline. A Site Independent Qualification Assessment (SIQA) will assess the validity of the participants' diagnosis and antidepressant treatment response for inclusion in the study.

All participants should continue their SSRI/SNRI antidepressant therapy throughout the entire study (see Section 6.8.1).

Prohibited medications will be stopped prior to the start of the OL Treatment Phase. Tapering or time of discontinuation of a prohibited medication prior to the start of the OL Treatment Phase should be based on drug's half-lives, potential drug-drug interactions, local prescribing information or clinical judgment (see Section 6.8 for details). Tapering and discontinuation of prohibited therapies should be initiated after completion of the second 17-item Hamilton Depression Rating Scale (HDRS-17) (Visit 1.2, see Section 1.3) assessment and the SIQA and confirmation these are passed. Eligible participants who do not require a tapered discontinuation of their prohibited treatment(s) can immediately proceed into the OL Treatment Phase. If needed (eg, longer tapering needed for prohibited therapies or other circumstances), the screening period may be extended up to 3 weeks after consultation with sponsor's medical monitor or designee.

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

examination including a brief neurologic examination, vital signs, 12-lead ECG, C-SSRS, urine drug test, alcohol breath test, and clinical laboratory tests) will be performed to assess eligibility. Menstrual cycle evaluation in premenopausal female participants will also be performed. Adverse events will be collected from the time a signed and dated informed consent form (ICF) is obtained until the completion of the last study procedure on the final Follow-up Visit.

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

Direct-entry participants meeting at baseline all of the inclusion (Section 5.1.2 and none of the exclusion criteria (Section 5.2.2) specific to them are eligible to proceed to the OL Treatment Phase.

4.1.3. Open-label Treatment Phase

Both transferred-entry and direct-entry participants will participate in this 52-week OL Treatment Phase.

For transferred-entry participants, assessments performed on Day 43 of the DB Treatment Phase of the parent study (Visit 2.7 of Studies MDD3001 or MDD3002) will not be repeated as part of this study. For these participants, the Day 43 visit of the parent study will coincide with Day 1 (OL Baseline, Visit 2.1) for the current study. There is no gap foreseen between the studies. Prior to conducting any study procedure for Study MDD3003, the investigator (or designated study personnel) will review and explain the written ICF to each transferred-entry participant. The ICF will be signed at the start of this phase (after completion of Day 43 in the parent study). After signing the ICF, transferred-entry participants will be evaluated to determine eligibility for study participation.

Transferred-entry participants should meet at baseline all eligibility criteria specific to transferred-entry participants (see Section 5.1 and Section 5.2). The End-of-treatment (EOT) Visit, ie, Visit 2.7 of Studies MDD3001 or MDD3002 can serve as baseline visit (Day 1) of this study.

All eligible participants (transferred- and direct-entry) will receive OL aticaprant treatment of one dose of 10 mg/day starting on Day 1 (OL Baseline). Transferred-entry participants (ie, from the DB short-term studies MDD3001 and MDD3002) will not be unblinded before commencement of OL aticaprant treatment; their treatment assignment in the short-term study will remain blinded until the database lock of the short-term study. The OL aticaprant treatment and use of the current SSRI/SNRI treatment will be captured in the participant paper diaries.

All eligible participants (transferred- and direct-entry) should take their assigned study intervention at home, once daily, from Day 1 through Week 52 (EOT), preferably in the morning.

Throughout the study, participants should continue their SSRI/SNRI antidepressant at an adequate dose (ie, at or above the minimum therapeutic dose per MGH ATRQ). See Section 6.8.1 for details.

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

All participants who discontinue study intervention during the OL Treatment Phase will have an EOT/Early Withdrawal (EW) Visit (Visit 2.14 in the Schedule of Activities [SoA]) and a Follow-up Visit (Visit 3.1 in the SoA) performed.

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

End-of-treatment/Early Withdrawal Visit

All participants will have an EOT/EW Visit (Visit 2.14 in the SoA) and a Follow-up Visit performed (Visit 3.1 in the SoA).

If a participant discontinues the study intervention, the EOT/EW Visit assessments (including MADRS) will be performed per the SoA, preferably on the day after the last dose. Entry to the Follow-up Phase should not be conducted for participants who withdraw consent for further study assessments; however, they are encouraged to complete the study assessments including the EOT/EW Visit if they are willing to do so.

4.1.4. Follow-up/End of Study Visit

All participants will return to the study site for a Follow-up Visit within 7 to 14 days after Visit 2.14 (EOT/EW). At the Follow-up Visit, safety and efficacy assessments/procedures will be completed per the SoA (see Section 1.3).

This phase will include all participants who have received at least 1 dose of study intervention (aticaprant) in this study.

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

4.1.5. Additional Details Related to Study Design

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

A diagram of the study design is provided in Section 1.2

4.1.6. Changes in Study-related Procedures as a Result of the COVID-19 Pandemic and Regional Crisis

The worldwide COVID-19 pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or study participants become potentially exposed to or infected with COVID-19. To assure the safety of study participants, maintain compliance with GCP, and minimize risks to study

integrity, if necessary, in consultation with the sponsor, the method of assessments may be changed (eg, paper assessments replaced by electronic assessments). In addition, site visits may be replaced with telephone, internet-based video conferencing applications, or home visits by qualified healthcare professionals (see Section 10.7). Rating scales/safety assessments can continue to be administered via video teleconferencing (MADRS) or phone (other assessments). Every effort should be made to complete the MADRS assessment via video teleconferencing and within the scheduled timeframe; if this cannot occur, the sponsor medical monitor or delegate should be contacted for direction. Normal procedures, as detailed in this protocol, will be resumed as soon as possible thereafter.

4.2. Scientific Rationale for Study Design

4.2.1. Study Population

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

Anhedonia, defined as an impaired capacity to experience or anticipate pleasure (Berrios 1995; Ho 2013) is a very common symptom of MDD, reported in ~75% of patients (Franken 2007) and is one of the required criteria for MDD (depressed mood and/or anhedonia) (Moayedoddin 2013; Schrader 1997). In addition to being a common symptom of MDD, as noted in the outset, it is a persisting dimension amongst individuals with MDD with inadequate response to SSRI/SNRI (Van Roekel 2017).

Data from the Phase 2 study 67953964MDD2001 showed greater reduction in overall depression severity on the MADRS in participants with MDD treated with 10 mg aticaprant added to ongoing antidepressant, compared with those who continued on just their current antidepressant plus placebo. CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

In contrast to available data about short-term antidepressant effects of aticaprant, less is known about safety with its long-term administration of and how the antidepressant effect evolves with long-term dosing. No studies have yet characterized long-term safety and the response to aticaprant when given longer than 6 to 8 weeks (Pizzagalli 2020). The safety of long-term use needs to be

systematically assessed with repeated dosing of aticaprant. This study will address the safety and efficacy of long-term administration of aticaprant.

The study will initially enroll participants through roll-over from 2 short-term efficacy studies MDD3001 and MDD3002 (transferred-entry participants). Transferred-entry participants who complete the 6-week DB Treatment Phase in either of the short-term studies (regardless of their treatment response) may participate in this study if this is clinically appropriate in the opinion of the investigator and provided they meet the specific eligibility criteria for transferred-entry participants (see Inclusion and Exclusion Criteria for transferred-entry participants in Sections 5.1.1 and 5.2.1, respectively).

Based on the targeted enrollment in the 2 short-term efficacy studies, it is anticipated that approximately 840 participants across all countries/territories (715 from the rest of the world [ROW], 80 from China and 45 from Japan [if participating]) will participate in the long-term safety study. Additionally, participants may be enrolled directly into the study to meet the target of achieving the required number of participants with 6 months and 1 year of exposure to aticaprant. Direct enrollment allows sites to enroll directly into the study at some point during the course of the study if additional number of participants are needed to support enrollment. The sponsor will notify the study sites when direct enrollment might be open (see Inclusion and Exclusion Criteria for transferred-entry participants in Sections 5.1.1 and 5.2.2, respectively).

The study population (transferred- and direct-entry) will include adult and elderly participants with MDD who have an inadequate response to their current standard-of-care antidepressant (SSRI/SNRI) who are moderately-to-severely depressed and with either moderate-to-severe anhedonia (MDD ANH+) or with mild or no anhedonia (MDD ANH-). Enrolling participants across the general MDD spectrum with MDD ANH+ and MDD ANH- allows a comprehensive characterization of the long-term safety profile of aticaprant and supports the generalizability of the safety findings. For the secondary and exploratory objectives, enrollment of MDD ANH+ and MDD ANH- populations facilitates the acquisition of long-term efficacy data for aticaprant as an adjunctive therapy to the current SSRI/SNRI treatment with inadequate response. Criteria defining MDD ANH+ and MDD ANH- will be described in an addendum to the protocol which will be blinded to the study sites.

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

4.2.2. RNA and CCI

CCI

CCI

CCI

CCI

4.2.3. Safety Assessments

Standard safety assessments including physical and neurological examination, vital signs, 12-lead ECG, clinical chemistry, hematology, and urinalysis will be performed. Additionally, emergence of suicidal ideation will be assessed using the C-SSRS ([Posner 2007](#)). The C-SSRS has been used frequently in clinical studies, and is a validated, standard measure for suicidal ideation assessment.

Sexual dysfunction is one of the most common side effects during the treatment of MDD with SSRI's/SNRI's. To investigate whether aticaprant has a further positive or negative effect on sexual function, the Arizona Sexual Experiences Scale ([McGahuey 2000](#)), will be used in this study.

4.2.4. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study, and during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled. Written consent/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 participant preferences.

Participants will be offered participation in optional pharmacogenomic research components including collection of blood samples for RNA analysis. Participants may decide to opt out of this optional research. The decision to opt out of either optional research component will not impact the eligibility to participate in the main study. Participants that take part in the optional research component(s) of the study will sign an additional ICF.

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

For participants who consent to the optional collection of real-world medical data, the sponsor is committed to protect their data and privacy. Tokenization and matching procedures will be utilized to allow for those participant's medical data to be obtained without violation of participant confidentiality (see Section 8.9). 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. All applicable applications used in this study are General Data Protection Regulation (GDPR)/Health Insurance Portability and Accountability Act (HIPAA) compliant.

The total blood volume to be collected is considered to be within the normal range allowed for this participant population over this time frame. The approximate blood volume to be collected is 114.5 mL for direct-entry participants and 103.0 mL for transferred-entry participants, which will be less than a Red Cross blood donation.

4.3. Justification for Dose

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. Phase 3 studies will assess a dosage of 10 mg/day as part of the primary analysis.

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 cleared and is primarily metabolized through CCI and CCI, which may provide rationale not to expect any age effect on the PK in the elderly participants.

4.4. End of Study Definition

4.4.1. End of Study Definition

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

For participants who complete the study (see definition Section 4.4.2) or who prematurely discontinue treatment early in the OL Treatment Phase, MDD treatment may be modified during the Follow-up Phase at the discretion of the investigator or participant's treating physician.

At the start of the Follow-up Phase, further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician and medication changes are permitted for participants.

4.4.2. Participant Study Completion Definition

The participant will be considered to have completed the OL Treatment Phase of the study if s/he has completed the MADRS assessment at the end of the 52-week OL Treatment Phase and did not discontinue study intervention prior to the completion of the OL Treatment Phase.

Participants are considered to have completed the Follow-up Phase if they have completed the Follow-up Visit (Visit 3.1 in the SoA).

Participants will be considered to have completed this study if they completed the OL Treatment Phase and the Follow-up Phase.

5. STUDY POPULATION

Screening for **direct-entry participants only** will be performed within 30 days before administration of the study intervention. Refer to Section 5.4 for conditions under which the repeat of any screening procedures are allowed. Efforts will be made for the inclusion of a diverse study population in terms of race, gender, and ethnicity.

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

5.1. Inclusion Criteria

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

5.1.1. Transferred-entry Participants

All participants who completed the 6-week DB Treatment Phase of Study MDD3001 or MDD3002, regardless of their response status, will be eligible to participate in this study, if they meet the study-specific eligibility criteria for transferred-entry participants.

1	Participants must have completed the DB Treatment Phase of Study 67953964MDD3001 (MADRS assessment at Day 43/Visit 2.7) or Study 67953964MDD3002 (MADRS assessment at Day 43/Visit 2.7) study without an early treatment discontinuation or switch in the oral SSRI/SNRI in the parent study
2	Participant must be medically stable on the basis of physical examination, medical history, vital signs (including blood pressure), and 12-lead ECG performed at baseline and prior to OL treatment initiation. The investigator's review of the machine read 12-lead ECG tracing is considered acceptable in determining participant's eligibility where the central cardiology results are not expected to be available before the need to begin dosing, or if actions need to be taken for safety reasons. 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.
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5.1.2. Direct-entry Participants

The following criteria apply only to those **participants entering directly into the study**. Each potential participant must satisfy all of the following criteria.

3	Male or female adult and elderly, 18 (or the legal age of consent if higher than 18 years of age, in the jurisdiction in which the study is taking place) to 74 years of age, inclusive.
4	Medically stable on the basis of physical examination (including a brief neurological examination), medical history, vital signs (including blood pressure), and 12-lead ECG performed at screening and baseline. If there are any abnormalities that are not specified in the inclusion and exclusion criteria, their significance must be determined by the investigator and recorded in the participant's source documents and initialed by the investigator.
5	Medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, re-testing of an abnormal laboratory value(s) that may lead to exclusion will be allowed once during the Screening Phase. The participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator.
6	Meet DSM-5 diagnostic criteria for recurrent or single episode MDD, without psychotic features (DSM-5 296.22, 296.23, 296.32, or 296.33), based upon clinical assessment and confirmed by the SCID-CT. Participants 65 years of age or older must have had the first onset of depression prior to 55 years of age.
7	Criterion modified per Amendment 1 7.1 Criterion modified per Amendment 2 7.2 Have had an inadequate response to at least 1 oral antidepressant treatment (see the inclusion criterion below), administered at an adequate dose (at or above the minimum therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current episode of depression. An inadequate response is defined as <50% reduction in depressive symptom severity but with some improvement (>0%) (ie, there may be minimal to moderate symptomatic improvement since the initiation of treatment, but some of the initial symptoms are still present, troubling to the participant and affecting behavior and function) as assessed by the MGH ATRQ. This must apply to the participant's current antidepressant treatment. Note: Medical/pharmacy/prescription records, a letter from a treating physician, etc can be used to verify the adequacy of the current antidepressant trial.

8	Criterion modified per Amendment 1 8.1 Criterion modified per Amendment 2 8.2 Is currently receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms at screening, in any approved formulation and available in the participating country/territory: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine at a stable dose (at or above the minimum therapeutic dose per MGH ATRQ) for at least 6 weeks. The current antidepressant cannot be the first antidepressant treatment for the first lifetime episode of depression. Note: The above SSRI/SNRI needs to be approved for the treatment of MDD according to the local label of the country/territory where the clinical site is located. Note: Medical/pharmacy/prescription records, a letter from a treating physician, etc can be used to verify the adequacy of the current antidepressant trial. The investigator will use this information to complete the MGH ATRQ. Note: Participants using fluvoxamine as current SSRI and have normal renal and hepatic function may enter the study.
9	Have a HDRS-17 total score of 20 or higher at the first and second screening interviews and must not demonstrate a clinically significant improvement (ie, an improvement of more than 20% on their HDRS-17 total score) between the first and the second independent HDRS-17 assessments.
10	BMI between 18 and 40 kg/m ² inclusive (BMI = weight/height ²).
11	Must be an outpatient at OL Treatment Phase baseline.
12	Participant's current major depressive episode, and antidepressant treatment response in the current depressive episode, must all be confirmed by the Site Independent Qualification Assessment.

5.1.3. All Participants (Direct-entry and Transferred-entry Participants)

13	Must sign an Informed Consent Form (ICF) indicating that he or she understands the purpose of and procedures required for the study and be willing to participate in the study.
14	Participants should not take any prohibited medication or food supplements as indicated in Section 6.8.
15	Criterion modified per Amendment 1 15.1 A female participant of childbearing potential must have a negative highly sensitive serum (β human chorionic gonadotropin [β-hCG]) pregnancy test at screening (direct-entry) and a negative urine pregnancy test at baseline and prior to initiation of the OL Treatment (all participants).
16	Criterion modified per Amendment 1

	16.1 A female participant must be (as defined in Section 10.5): • Not of childbearing potential • Of childbearing potential and – Practicing a highly effective, preferably user independent method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 4 weeks after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, non-compliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.5.
17	Criterion modified per Amendment 1 17.1 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.
18	During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 3 months) after receiving the last dose of study intervention: • A male participant must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/cream/suppository) when engaging in any activity that allows for passage of ejaculate to another person. • A male participant who is sexually active with a woman who is pregnant must use a condom. Male participants should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak.
19	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.

5.2. Exclusion Criteria

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

5.2.1. Transferred-entry Participants

1	Participant has been non-compliant with the study intervention administration in the DB Treatment Phase in either of Studies 67953964MDD3001 or 67953964MDD3002 (ie, have missed either 4 or more consecutive doses of study intervention or a total of 8 or more doses during the DB Treatment Phase)
2	The evaluation of the benefit versus risk of continued aticaprant treatment is not favorable for the participant in the opinion of the investigator.

3	Participant is reporting suicidal ideation with intent to act or suicidal behavior at baseline.
4	Participant has taken any prohibited therapies that would not permit dosing on Day 1, as noted in the pre-study and concomitant therapy section.
5	Participant 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.

5.2.2. Direct-entry Participants

6	Criterion modified per Amendment 1 6.1 Criterion modified per Amendment 2 6.2 Have had in the current depressive episode, no response (treatment failure) to 5 or more antidepressant treatments including the current SSRI/SNRI (ie, the one presumed to be continued in the treatment phase) assessed using the MGH ATRQ.
7	Has one or more of the following diagnoses: • A DSM-5 diagnosis (which has been the primary focus of psychiatric treatment within the past 2 years) of: – panic disorder – generalized anxiety disorder – social anxiety disorder – specific phobia These are allowed as secondary diagnoses if MDD is the primary focus of treatment according to the investigator. • A current (in the past year) DSM-5 diagnosis of: – obsessive-compulsive disorder (OCD) – post-traumatic stress disorder (PTSD) – anorexia nervosa – bulimia nervosa Note: These disorders need to be under control and stable for at least 1 year for the participant to be enrolled. • A current or prior (lifetime) DSM-5 diagnosis of: – a psychotic disorder or MDD with psychotic features – bipolar or related disorders (confirmed by the SCID-CT)

	– intellectual disability (DSM-5 diagnostic codes 317, 318.0, 318.1, 318.2, 315.8, and 319) – autism spectrum disorder – borderline personality disorder – antisocial personality disorder – histrionic personality disorder – narcissistic personality disorders – somatoform disorders
8	Known allergies, hypersensitivity, or intolerance to aticaprant or any of its excipients (refer to the IB).
9	Has a history or evidence of clinically meaningful noncompliance with current antidepressant therapy.
10	Has a history of moderate-to-severe substance use disorder including alcohol use disorder according to DSM-5 criteria within 6 months before screening.
11	Has received an investigational intervention (including investigational vaccines) or used an invasive investigational medical device within 60 days or 10 half-lives, whichever is longer, before the start of the Screening Phase, or has participated in 2 or more MDD or other psychiatric condition clinical interventional studies (with different investigational medication) in the previous 1 year before the start of the Screening Phase or is currently enrolled in an investigational study.
12	Criterion modified per Amendment 2 12.1 Has had in the current episode an inadequate response to adequate course of intravenous or intranasal ketamine or esketamine, electroconvulsive therapy (ie, at least 7 treatments), vagal nerve stimulation, or a deep brain stimulation device.
13	Has a current homicidal ideation/intent, per the investigator's clinical judgment, or has suicidal ideation with some intent to act within 3 months prior to the start of the Screening Phase, per the investigator's clinical judgment or based on the Columbia Suicide Severity Rating Scale (C-SSRS), corresponding to a response of "Yes" on Item 4 (active suicidal ideation with some intent to act, without specific plan) or Item 5 (active suicidal ideation with specific plan and intent), or a history of suicidal behavior within the past year prior to the start of the Screening Phase. Participants reporting suicidal ideation with intent to act or suicidal behavior prior to the start of the OL Treatment Phase should be excluded.
14	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). Participant aged ≥ 65 years: has a Mini

	Mental State Examination (MMSE) <25 or <23 for those participants with less than high school equivalent education.
15	Has current, or a history (past 6 months) of seizures.
16	Criterion modified per Amendment 1 16.1 Has clinically significant 12-lead ECG abnormalities at the start of the Screening Phase or on Day 1 of the OL Treatment Phase prior to the first aticaprant dose that may jeopardize the participants' safety or the integrity of the study, in the investigator's judgment, defined as: - During screening and/or Day 1 (pre-dose), a QT interval corrected according to Fridericia's formula (QTcF): ≥ 450 msec (male participants); ≥ 470 msec (female participants). Note: If the QTcF is prolonged on the initial 12-lead ECG at a given time point, the average QTcF of 3 12-lead ECGs, recorded 4 minutes apart, must not be ≥ 450 msec for male participants and ≥ 470 msec for female participants. - On Day 1 (pre-dose), a QT interval corrected according to Fridericia's formula (QTcF): ≥ 450 msec (males) or ≥ 470 msec (female participants) based on the site-evaluated ECG; if the QTcF is prolonged on the initial ECG, the average QTcF of 3 ECGs, recorded 4 minutes apart, must not be ≥ 450 msec for males and ≥ 470 msec for female participants. - Evidence of second and third degree atrioventricular (AV) block, complete left bundle branch block (LBBB), or complete right bundle branch block (RBBB). - Features of new ischemia. - Arrhythmia (except premature atrial contractions [PACs] and premature ventricular contractions [PVCs]).
17	Participant has a history of additional risk factors for Torsades de Pointes (eg, heart failure, hypokalemia, family history of long QT syndrome)
18	Has a history of, or symptoms and signs suggestive of, liver cirrhosis (eg, esophageal varices, ascites, and increased prothrombin time) OR alanine aminotransferase (ALT) or aspartate aminotransferase (AST) values $\geq 3 \times$ the upper limit of normal (ULN) or total bilirubin $> 1.5 \times$ the ULN in the Screening Phase. Repeat of screening test for abnormal ALT and AST is permitted during the screening period provided per investigator discretion and provided there is an alternative explanation for the out-of-range value. For elevations in bilirubin if, in the opinion of the investigator and agreed upon by the sponsor's medical officer, the elevation in bilirubin is consistent with Gilbert's syndrome, the participant may participate in the study.
19	Criterion Modified per Amendment 2

	19.1 Has positive test result(s) for alcohol and/or drugs of abuse (eg, opiates [including methadone], cocaine, amphetamines, methamphetamines, cannabinoids, cannabidiol [CBD], phencyclidine [PCP], barbiturates, 3,4-Methylenedioxymethamphetamine [MDMA]) at screening or baseline. Note: One retest during screening is allowed at investigator's judgment. Tobacco and caffeine use are not exclusionary. - Participants who have a positive test result at screening due to prescribed psychostimulants taken for any indication must discontinue the medication (if considered clinically appropriate) at least 2 weeks before Day 1 of the OL Treatment Phase. The result of the Day 1 test (performed on-site) for drugs of abuse must be negative. - Otherwise, participants who have a positive test result at screening due to prescribed/over-the-counter opiates or barbiturates may be permitted to continue in the Screening Phase if the medication is discontinued at least 1 week or 5 half-lives, whichever is longer, before Day 1 of the OL Treatment Phase. The result of the Day 1 test (performed on-site) for drugs of abuse must be negative. - Intermittent use of cannabinoids and/or alcohol prior to the start of the Screening Phase is not exclusionary as long as the participant does not meet the criteria for substance use disorder. A positive test for cannabinoids and/or alcohol at the start of the Screening Phase is not exclusionary; however, a positive test (performed on-site) result for either of these on Day 1 of the OL Treatment Phase is exclusionary. - Retesting is not permitted for positive test result(s), except for reasons stated above.
20	Has severe renal impairment (creatinine clearance <30 mL/min).
21	Has a recent (last 3 months) history of, or current signs and symptoms of: - Uncontrolled Type 1 or Type 2 diabetes mellitus. Note: Participants with Type 1 or Type 2 diabetes mellitus who are controlled (hemoglobin A1c ≤9.0%) may be eligible to participate if otherwise medically healthy, and if on a stable regimen of glucose-lowering medications for at least 2 months prior to screening). - Clinically significant or unstable cardiovascular, respiratory, gastrointestinal, neurologic, hematologic, rheumatologic, immunologic or endocrine disorders.
22	Has current signs/symptoms of hypothyroidism or hyperthyroidism. For participants with a history of thyroid disease and for participants who, regardless of thyroid history have the thyroid-stimulating hormone (TSH) value out of range, a free thyroxine (FT₄) test will be conducted. If the FT₄ value is abnormal and considered to be clinically significant (after discussion with the sponsor's study responsible physician/scientist or designee) the participant is not eligible. Participants with a pre-existing history of thyroid disease/disorder who are treated with thyroid hormones need to be on a stable dosage for 3 months prior to the start of the Screening Phase. Participants taking thyroid supplementation for antidepressant purposes are not allowed in the study.

23	Has Cushing's disease, Addison's disease, primary amenorrhea, or other evidence of significant medical disorders of the hypothalamic-pituitary-adrenal axis.
24	Has significant medical illness, particularly unstable medical problem (to be reviewed with the sponsor's medical monitor).
25	Has a known history (past 6 months) of peptic ulcer, or history (lifetime) of upper gastrointestinal bleeding, or known untreated <i>Helicobacter pylori</i> infection, or a diagnosis of Zollinger-Ellison syndrome (ZES).
26	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).
27	Has taken any prohibited therapies that would not permit dosing on Day 1.
28	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.
29	Ongoing psychological treatments (eg, Cognitive Behavioral Therapy, Interpersonal Psychotherapy, Psychodynamic Psychotherapy etc), initiated within 6 weeks prior to start of screening. Note: a participant who has been receiving ongoing psychological treatment for a period of greater than 6 weeks is eligible, if the investigator deems the psychological treatment to be of stable duration and frequency.
30	Criterion modified per Amendment 1 30.1 Is a female participant who is pregnant, breastfeeding, or planning to become pregnant while enrolled in this study or within 6 weeks after the last dose of the study intervention.
31	Plans to father a child while enrolled in this study or within 3 months after the last dose of study intervention.
32	Has a diagnosis of acquired immunodeficiency syndrome (AIDS). Human immunodeficiency virus testing is not required for this study.
33	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.
34	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.

Investigators should ensure that, all study enrollment criteria have been met prior to Day 1 of the OL Treatment Phase (for direct- and transferred-entry participants). If a participant's status changes (eg, laboratory results or receipt of additional medical records) after the start of screening but before the first dose of study intervention is given in this study, such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. The

sponsor will evaluate and approve/reject requests for re-screening an individual participant on a case-by-case basis.

5.3. Lifestyle Considerations

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

1. Participants should not take any prohibited medication or food supplements. Refer to Section 6.8.2 for details regarding prohibited and restricted therapy during the study.
2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (eg, contraceptive requirements).

5.3.1. Meals and Dietary Restrictions

1. The use of limited amounts of alcohol (up to 2 standard drink consumptions daily) will be allowed but not within 24 hours before any study visit. A standard drink is defined as: a 350-mL glass of 5% alcohol-by-volume (ABV) beer (1.7 units), a 150-mL glass of 12% ABV wine (2 units), or a 45-mL glass of a 40% ABV (80 proof) spirit (1.7 units).
2. Should not consume food or beverages containing grapefruit juice, Seville oranges (including any orange marmalade), or quinine (eg, tonic water) from 24 hours (72 hours in the case of grapefruit juice and Seville oranges) before the first dose of study intervention and throughout the duration of the study until the last dose of study intervention.

5.3.2. Activity

1. Participants should abstain from strenuous exercise within 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during the study (eg, watching television, reading).
2. Participants should be advised not to donate blood during the study and for at least 3 months after completion of the study.

5.4. Screen Failures

Participant Identification, Enrollment, and Screening Logs - Direct-entry Participants Only

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

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made.

All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent.

Limited re-testing of abnormal screening values, including laboratory values, vital signs, and 12-lead ECGs that potentially lead to exclusion are allowed using an unscheduled visit during the screening period to reassess eligibility. Individuals who do not meet the criteria for participation in this study (screen failure) but in the future are expected to meet the eligibility criteria, may be rescreened on one occasion only. This should be discussed with and approved by the sponsor's study responsible physician/scientist prior to re-screening.

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

Not applicable for this study.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Designation	Product
Investigational Medicinal Product	Aticaprant / JNJ-67953964 (10 mg)
Non-investigational Medicinal Product/Auxiliary Medicinal Product	SSRI/SNRI antidepressant*

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

* Oral SSRI/SNRI antidepressant therapy should be continued at an adequate dose (ie, at or above the minimum therapeutic dose per the MGH ATRQ) throughout the entire study, unless a significant tolerability issue occurs, in which case the oral SSRI/SNRI antidepressant may be discontinued and if appropriate, switched to a new SSRI/SNRI antidepressant (see Section 6.8.1). The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. For further information regarding their use, refer to the relevant local prescribing information.

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Aticaprant will be supplied as film-coated tablets of 10 mg. The daily intake is 1 tablet.

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

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

During the OL Treatment Phase, all participants must take 1 tablet of aticaprant once daily, around the same time and preferably in the morning. The first dose will be taken by the participant at the study site on Day 1 of the OL Treatment Phase. Thereafter, study intervention will be taken at home by the participant for daily self-administration until next clinical site visit. For clinical site visits, participants will be asked not to take study intervention in the morning before they come to

the site for the visit. The study intervention will be self-administered on-site and witnessed by the investigator or a properly trained designee. The investigator or designated study personnel will maintain a log of all study intervention dispensed and returned. Drug supplies will be inventoried and accounted for throughout the study. Tablet counts of study intervention will be performed at each clinical visit during the treatment phase of the study.

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

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

Participants should also continue to take their SSRI/SNRI antidepressant (the Non-investigational Medicinal Product) at an adequate dose (ie, at or above the minimum therapeutic dose per the MGH ATRQ), throughout the entire study (see Section 6.8.1), unless significant tolerability issue occurs, in which case the oral SSRI/SNRI antidepressant may be discontinued and switched to a new SSRI/SNRI antidepressant. The participant's SSRI/SNRI antidepressant therapy during the study should be captured in a medication diary (see Section 6.8.1 for SSRI/SNRI antidepressant therapy). If appropriate, additional details may be provided in a pharmacy manual/study site Investigational Product (IP) manual that is provided separately and noted in Section 8.

Description of Interventions

Group/Arm Name	Group/Arm A
Intervention Name	Aticaprant / JNJ-67953964
Dose Formulation	Film-coated tablet
Unit Dose Strength(s)	Available unit dose strength: 10 mg
Dosage Level(s) and Frequency	Participants will receive 10 mg aticaprant orally once daily in addition to their SSRI/SNRI, which will be continued during the entire study.
Route of Administration	☒ Oral ☐ IV infusion ☐ IV injection ☐ Intramuscular ☐ Other
Dosing Instructions	Participants must take 1 oral film-coated tablet once daily, preferably in the morning.
Use	☒ Experimental ☐ Background intervention ☐ Challenge agent ☐ Diagnostic ☐ Other
Investigational Medicinal Product (IMP)	☒ Yes ☐ No
Non-Investigational Medicinal Product/Auxiliary Medicinal Product (NIMP/AxMP)	☐ Yes ☒ No

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Preparation/Handling/Storage

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

6.2.2. Accountability

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

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

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

6.3. Measures to Minimize Bias: Randomization and Blinding

There will be no randomization for participants enrolled in this study. All direct-entry participants who meet the entry criteria will start with aticaprant 10 mg and should continue their current oral antidepressant medication. Transferred-entry participants who join this study will start with aticaprant 10 mg (regardless of their treatment assignment in the short-term study which will remain blinded) and should continue the same oral current antidepressant medication that they were receiving in the parent short-term study.

6.4. Study Intervention Compliance

Except for on-site clinic visits, the study intervention will be self-administered by participant at home daily at the same time preferably in the morning from Day 1 to Week 52 of the OL treatment. The first dose will be taken on Day 1 on-site and will be witnessed by the investigator or a responsible designee. At subsequent clinical visits, study intervention will be self-administered on-site and witnessed by the responsible site staff personnel. Participants will receive instructions on compliance with the study intervention treatment. During the study, the investigator or designated study site personnel will be responsible for providing additional instruction to re-educate any participant to ensure compliance with taking the study intervention. Participant paper diary will be provided to capture study intervention use and reviewed by the investigator or a responsible designee as specified in the SoA schedule (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 post-baseline visits. Participants with repetitive noncompliance to the study intervention in the OL Treatment Phase may be withdrawn from study intervention (see Section 7). Missing study intervention doses due to temporary interruption (eg, adverse event, per Section 7.1.4 or other clinically relevant reason) will not be considered non-compliance.

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.

6.5. Dose Modification

This is a fixed dose study of aticaprant 10 mg per day.

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

There is no provision of aticaprant following the end of OL Treatment Phase. Participants will be instructed that aticaprant will not be made available to them after they have completed the OL Treatment Phase (Week 52). Further clinical/standard of care for the treatment of depression will be arranged by the study investigator and/or the participant's treating physician.

6.7. Treatment of Overdose

For this study, any dose of aticaprant greater than 30 mg aticaprant 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/serious adverse events (SAEs) and laboratory abnormalities until aticaprant can no longer be detected systemically (at least 2 days).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.
- Overdose should be reported in the eCRF as an AE.

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

6.8. Concomitant Therapy

Pre-study non-antidepressant therapies administered up to 30 days before the start of the Screening Phase must be recorded at the start of this phase. Ongoing (chronic or occasional) administration and known prior (past 6 months) use of CCI must be recorded (eg, dose, duration, reason) under Concomitant Therapies in the eCRF.

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

Direct-entry participants taking antidepressant medications which are not listed on the MGH ATRQ (refer to Section 10.8 for a list of medications used for the treatment of depression to be discontinued during the Screening Phase) at entry will have these medications tapered (if applicable) and discontinued during this phase, per the local prescribing information or clinical judgment. Additionally, any medication that is listed on the MGH ATRQ and is being taken in addition to the current SSRI or SNRI in the study OL Treatment Phase inclusive medications taken for reasons other than depression (eg, insomnia, anxiety) should be continued during the Screening Phase but must be discontinued before the start of the OL Treatment Phase.

Tapering and discontinuation of prohibited therapies should be initiated after completion of the second HDRS-17 (see Section 1.3, SoA, Visit 1.2) assessment and the SIQA and confirmation these were passed. Eligible participants who do not require a tapered discontinuation of their prohibited treatment(s) can proceed to the baseline visit.

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

Participants should continue to take their permitted concomitant medications at their regular schedule; however, restrictions as outlined in Sections 6.8.2 and 10.8 should be taken into account.

Participants receiving psychotherapy (including cognitive behavioral therapy; CBT), may continue receiving psychotherapy. New psychotherapy or changes to the ongoing psychotherapy, is allowed during the OL Treatment Phase. Any change in existing therapy or new therapy must be documented on the concomitant therapies form.

This study allows the use of locally approved (including emergency use-authorized [or country/territory specific equivalent emergency use approved]) COVID-19 vaccines. For participants who receive an approved or authorized vaccine, it is recommended that this occurs at least 5 days prior to the start of dosing. If any vaccines (COVID-19 or other vaccines, eg, influenza) are administered, these should be recorded in the source documents and entered in the eCRF.

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

6.8.1. SSRI/SNRI Antidepressant Therapy

Participants should continue to take their SSRI/SNRI antidepressant at an adequate dose (ie, at or above the minimum therapeutic dose per the MGH ATRQ) throughout the entire study (see below for a list of antidepressants), unless significant tolerability issue occurs, in which case the oral SSRI/SNRI antidepressant may be discontinued and switched to a new SSRI/SNRI antidepressant (from those listed below). The proposed change and the reason must be discussed with sponsor's study responsible physician/scientist or designee and documented in the eCRF. The following antidepressants are permitted: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, and desvenlafaxine. Participants will only continue 1 oral SSRI/SNRI antidepressant (ie, monotherapy) to which aticaprant will be added.

Participants will receive instructions on compliance with their oral SSRI/SNRI antidepressant treatment. 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 SSRI/SNRI oral antidepressant. During the screening phase (direct-entry participants only), compliance to the current antidepressant treatment must be confirmed by documented records (eg, medical/pharmacy/prescription record, a letter from a treating physician, etc). During the OL Treatment Phase, the compliance to the ongoing 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. A participant's diary will be provided to capture the current oral antidepressant (SSRI/SNRI) use (see Section 1.3).

The SSRI/SNRI 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 study responsible physician/scientist or designee.

6.8.2. Prohibited Therapies

A list of prohibited concomitant therapies is provided in Section 10.8. This list is not all-inclusive; if necessary, please contact the medical monitor for any questions regarding a medication(s).

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

Except where specifically noted, the prohibited medications listed in Section 10.8 are prohibited from 1 week (or 5 half-lives, whichever is longer) prior to the first dose of study intervention until after the last dose of study intervention.

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

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

In addition:

- Electroconvulsive therapy (ECT), deep brain stimulation (DBS), TMS, and vagus nerve stimulation (VNS) are prohibited.
- Participants taking benzodiazepines and/or permitted non-benzodiazepine sleep medications (eg, zolpidem, zaleplon) during the Screening Phase can continue these medications (at dosages equal to or less than the equivalent of 4 mg/day of lorazepam), No dose increases beyond the equivalent of 4 mg/day of lorazepam, or a start of new benzodiazepine medications are permitted during the OL Treatment Phase. A positive urine drug test for use of PCP, or cocaine from Day 1 through the final visit in the OL Treatment Phase will lead to discontinuation from the study (see Section 7).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

If a participant discontinues study intervention or withdraws from the study before the end of the OL Treatment Phase, the EOT/EW assessments must be obtained.

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- Lack of efficacy, per investigator's judgment.

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

For any participant who has not completed OL Treatment Phase (Week 52 visit or at least Week 52 MADRS assessment), an EOT/EW Visit (ie, Visit 2.14) should be conducted as soon as possible, preferably within one day of the last dose of study intervention, followed by the Follow-up Phase (Visit 3.1). Participants will be considered to have completed the Follow-up Phase if he or she has completed the Follow-up Visit.

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

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

7.1.1. Withdrawal of Consent

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 Follow-up Visit. A participant declining to return for scheduled visits does not necessarily constitute withdrawal of consent. Alternate follow-up mechanisms that the participant agreed to when signing the consent form apply as local regulations permit.

7.1.2. 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 $>5 \times$ ULN at least twice over a 2-week period, AST and/or ALT $\geq 3 \times$ ULN and total bilirubin exceeds $\geq 2 \times$ ULN (confirmed by repeat testing), or one of the conditions outlined in Section 10.6 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.1.3. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline Day 1 [OL Baseline, Visit 2.1] for the current study) in QT interval corrected using Fridericia's

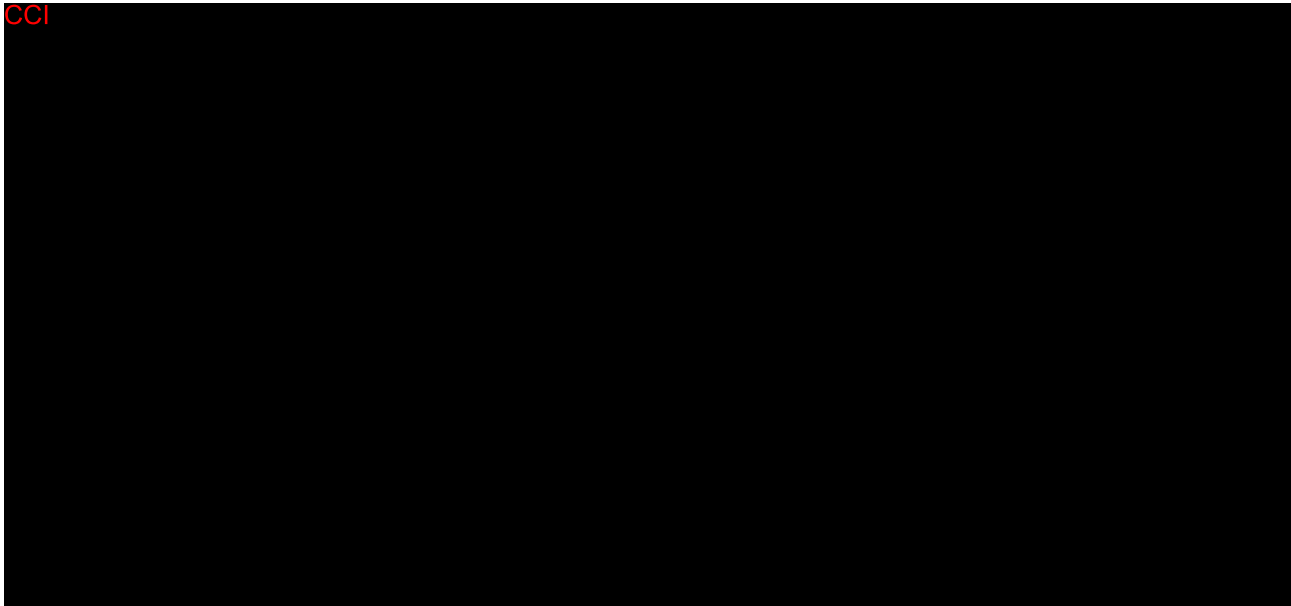
formula (QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the 12-lead ECG printed at the time of collection must be documented. Any new clinically relevant finding must be reported as an AE. The QTc stopping criteria apply only to the OL Treatment Phase and not at screening or baseline.

A participant who meets either of the following criterion (after baseline Day 1, pre-dose) based on the average of triplicate 12-lead ECG readings will be withdrawn from study intervention.

- QTcF change from baseline is ≥ 60 msec AND QTcF > 480 msec
- OR
- QTcF > 500 msec

7.1.4. Treatment Interruptions, Restart, or Re-Challenge

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7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up,
- Major Protocol Deviation (to be assessed on a case-by-case basis),
- Withdrawal of consent. (**Note:** “Withdrawal of Consent” should only be selected as a reason for withdrawal if the participant does not agree to any further study assessments or procedures. If the participant is agreeable to participating in the EOT/EW visit and the Follow-up Phase, another reason for withdrawal should be selected). When a participant withdraws consent, every effort should be made to determine if the cause of withdrawal was due to tolerability or lack of efficacy,
- Positive urine drug test for PCP or cocaine at any time point during the study,
- Death.

When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed. Study intervention assigned to the withdrawn participant may not be assigned to another participant.

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

7.2.1. Withdrawal of Consent

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

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

7.2.2. Withdrawal From the Use of Research Samples

Withdrawal From the Optional Research Samples While Remaining in the Study

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

Withdrawal From the Use of Genetic Research Samples (RNA)

A participant who withdraws their consent from the use of RNA samples obtained in the study will have the following options regarding the optional research sample:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.

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

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

Withdrawal From the Use of Samples in Future Research

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

7.3. Lost to Follow-up

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 eCRF.
- 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 safety, efficacy, laboratory, pharmacogenomics (RNA) and biomarker, measurements applicable to this study.

Order of Assessments

All MADRS assessments will be performed by qualified site-based raters using videoconferencing which provides opportunity to schedule and complete the MADRS assessment before or after the on-site visit but respecting the visit window. To reduce the time spent by a participant at the study

site during clinical visits with several study procedures, the sites are recommended to consider conducting the MADRS assessment (with video conferencing) outside of the on-site visit.

Patient-reported outcome (PRO) assessments should be completed by participants in the order stated in the SoA and in a language in which the participant is fluent and literate. Study personnel will instruct participants how to self-complete the PRO assessment (Section 10.9) and further details are provided in a separate manual provided to the site. When possible, PRO assessments that have not been completed at home prior to the study visit but are conducted when the participant is on-site, together with the on-site PRO assessments, should be completed before any study tests, procedures, or other consultations to prevent influencing participant perceptions. However, during site visits with fasting blood sampling, this may not be possible and for these visits it is recommended that procedures should be performed in the following sequence:

- Blood and urine collection (when in fasted condition), dosing, breakfast, PROs, interview with site-based rater (SIGMA via videoconference, if not completed before the actual visit, CGI-S), C-SSRS, and safety assessments.
- If blood sampling or vital sign measurement is scheduled for the same time point as 12-lead ECG recording, the procedures are recommended to be performed in the following order: 12-lead ECG, vital signs, blood draw.
- Additional serum (by central laboratory) or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Twelve-lead ECG readings will be performed pre-dose at Visit 2.1 (Day 1). For additional 12-lead ECG readings, refer to the SoA.

The total blood volume for the study is approximately 114.5 mL for direct-entry participants and 103.0 mL for transferred-entry participants. 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
Direct-entry Participants			
Safety (including screening and post-intervention assessments)			
- Hematology and serum chemistry ^b	4.5	7	31.5
- TSH/Free T4	2.5	1	2.5
- Lipid panel	2.5	1	2.5
Antidepressant compliance	2.0	4	8.0
Biomarker samples (plasma and serum)	20.0	3	60.0
RNA samples ^c	5.0	2	10.0
Approximate Total (Direct-entry)^d	36.5	18	114.5
Transferred-entry Participants^e			
Safety			
- Hematology and serum chemistry ^f	4.5	6	27.0
Antidepressant compliance	2.0	3	6.0
Biomarker samples (plasma and serum)	20.0	3	60.0
RNA samples ^c	5.0	2	10.0
Approximate Total (Transferred-entry)^d	31.5	14	103.0
Abbreviations: FT4 = free thyroxine; HbA1c = Hemoglobin A1c; RNA = ribonucleic acid; TSH = thyroid-stimulating hormone; β -hCG = beta human chorionic gonadotropin.			

- Calculated as number of samples multiplied by amount of blood per sample.
 - Glycated hemoglobin (HbA1c) is taken with hematology if at the same visit.
Serum β -hCG pregnancy test at Visits 1.1, 2.1, 2.4, 2.7, 2.10, 2.13, and 2.14 and is taken with serum chemistry.
Lipid testing is taken with serum chemistry at Visits 1.1, 2.1, 2.4, 2.7, 2.10, 2.13, and 2.14.
 - Blood samples will be collected only from participants who have consented to provide an optional RNA sample[s] for research.
 - Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
 - For transferred-entry participants, the Day 43 of the DB Treatment Phase in the parent study (ie, MDD3001 or MDD3002) will coincide with the OL baseline (Visit 2.1) for this study. Assessments performed on Day 43 of the parent study will not be repeated as part of Visit 2.1. The number of samples and the volume of blood might be lower than indicated above.
 - Glycated hemoglobin (HbA1c) is taken with hematology if at the same visit.
Serum β -hCG pregnancy test at Visits 2.4, 2.7, 2.10, 2.13, and 2.14 is taken with serum chemistry.
Lipid testing is taken with serum chemistry at Visits 2.4, 2.7, 2.10, 2.13, and 2.14.
- Note: An indwelling intravenous cannula may be used for blood sample collection.

Sample Collection and Handling

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

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

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

Study-specific Materials

The investigator will be provided with the following supplies:

- IB for aticaprant
- Data Science Materials
- Investigational Product (IP) Binder, including the IP Procedures Manual
- Laboratory manual and materials
- Guidance on the recommended order of study procedures
- MGH ATRQ Guidance document
- 12-lead ECG equipment and associated materials (eg, manual)
- Rater qualifications/requirements for select clinician-administered assessments
- Clinician-administered and Patient-reported outcome assessments:
 - Paper versions, as applicable
 - Electronic devices and associated materials
- Procedural documents for SIQA
- Procedural documents for independent, central rater and remote rater interviews
- eCRF Completion Guidelines
- Sample ICF
- Interactive web response system (IWRS) manual
- Participant recruitment materials
- Participant paper diaries
- Engage: A Smartphone Application used for video and audio teleconferencing

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

8.1. Efficacy Assessments

The efficacy assessments will be performed at the timepoints indicated in the SoA (Section 1.3). It is recommended that the raters for the efficacy assessments not be involved in study intervention dosing, AE assessments, or other safety evaluations.

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

All PRO instruments will be available for regulators and for IRB/IEC submissions and will be provided separately in a companion manual with the instruments that will be submitted with the protocol. The PRO and AE data will not be reconciled with one another.

8.1.1. **Montgomery-Åsberg Depression Rating Scale (MADRS)**

The 10-item clinician-administered MADRS was designed to be used in participants with MDD to measure the overall severity of depressive symptoms ([Montgomery 1979](#)). The MADRS scale has been selected as the primary efficacy measure for this study because it is validated, reliable, and acceptable to regulatory health authorities as a primary scale to determine efficacy in major depression. The MADRS be administered using the Structured Interview Guide for the MADRS (SIGMA).

The primary efficacy evaluation will be the MADRS total score. The MADRS is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment. The scale consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total score of 60. Higher scores represent a more severe condition. The MADRS evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel (interest level), pessimistic thoughts, and suicidal thoughts. The test exhibits high inter-rater reliability.

The MADRS will be performed by site-based raters via video-recording during the study using the SIGMA. The typical recall period for the MADRS is 7 days. MADRS assessments may be video-recorded for the purpose of quality monitoring.

8.1.2. **CCI**

CCI

8.1.3. **Snaith-Hamilton Pleasure Scale (SHAPS)**

The SHAPS ([Nakonezy 2010](#), [Snaith 1995](#)) is a self-report 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](#)).

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

The CGI-S 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.

8.1.5. CCI [REDACTED]

CCI [REDACTED]

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

The 9-item 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.

8.1.7. CCI [REDACTED]

CCI [REDACTED]

8.1.8. CCI [REDACTED]

CCI [REDACTED]

CCI [REDACTED]
[REDACTED]

8.1.9. CCI [REDACTED]
[REDACTED]

CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

8.1.10. CCI [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

8.1.11. CCI [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

In this study, this assessment will be performed only in the direct-entry participants and in those transferred from Study MDD3001.

8.1.12. CCI [REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

In this study, this assessment will be performed only in the direct-entry participants and in those transferred from MDD3001.

8.1.13.

CCI

8.2. Other Assessments - Screening Only

8.2.1. Hamilton Depression Rating Scale (HDRS-17)

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

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

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

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

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

8.2.4. Site Independent Qualification Assessment (SIQA)

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

8.3. Safety Assessments

An IDMC will be commissioned for this study. Details regarding the IDMC are provided in Section 10.3.6, Committees Structure.

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 neurological examination. Height will be measured at screening only. Body weight will be measured at screening and throughout the study according to the SoA.

Body weight should be measured using a calibrated scale at each indicated visit. 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 Baseline (Day 1, pre-dose) until 4 regular consecutive complexes are available in good readable quality.

Notes:

- During screening (for direct-entry participants only), if QTcF is prolonged on the initial ECG (ie, ≥ 450 msec [males] or ≥ 470 msec [females]) the average QTcF of three 12-lead ECGs, recorded 4 minutes apart, must not be ≥ 450 msec for male participants and ≥ 470 msec for female participants.
- At Visit 2.1 (Day 1), if QTcF is prolonged based on-site evaluated ECG, a total of three 12-lead ECGs should be obtained at least 4 minutes apart. The average QTcF of the three 12-lead ECGs will then be used to determine the participant's eligibility.
- During the OL Treatment Phase, if a clinically significant finding is identified in QTcF, the average QTcF of three ECGs, recorded 4 minutes apart, will be used to assess QTc stopping criteria (see Section 7.1.3, QTc Stopping Criteria).

During the collection of 12-lead 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 12-lead 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 12-lead ECG recording, the procedures should be performed in the following order: 12-lead ECG(s), vital signs, blood draw. Blood pressure and pulse/heart rate measurements will be assessed supine using a completely automated device. Manual techniques will be used only if an automated device is not available. Supine 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).

8.3.4. Clinical Safety Laboratory Assessments

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

Clinical laboratory assessments, including TSH (all participants, at screening only), follicle stimulating hormone (FSH) (female participants only, at screening only if required for documentation that a female participant is not of childbearing potential, see Inclusion Criterion 16), FT₄, hematology, serum chemistry, glycated hemoglobin (HbA1c), lipid panel, and urinalysis that should be performed at approximately the same time under fasting conditions, except possibly at the Screening Visit. The clinical laboratory assessments, 12-lead ECGs and vital signs should be done first and then food or coffee provided before PROs and clinician-rated observations are carried out.

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 and urine pregnancy tests may be conducted as needed per the investigator's judgment.

8.3.6. 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.

8.3.7. 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 for the direct-entry participants only. 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 to screening in the eCRF. 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 of study entry.

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.

8.3.8. Arizona Sexual Experiences Scale (ASEX)

The ASEX is a patient-reported 5-item rating scale, which will be used to quantify sex drive, arousal, vaginal lubrication/penile erection, ability to reach orgasm, and satisfaction from orgasm. Response options are a 6-point Likert scale ranging from hyperfunction (1) to hypofunction (6). Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. ASEX designates “sexual dysfunction” when the total score is 19 or higher; or when any single item has a score of 5 or 6; or when any three items each have a score of 4 or higher. The scale has shown satisfactory reliability and validity (McGahuey 2000). The ASEX has a recall period of the past week.

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

The MMSE test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. It is commonly used in medicine and allied health to screen for dementia. The test is divided into 2 sections: the first section requires vocal responses and covers orientation, memory, and attention. The second part assesses ability to name, follow verbal and written commands, write a sentence spontaneously, and copy a complex polygon similar to a

Bender-Gestalt Figure. The score ranges from 0 (minimum score) to 30 (maximum score) and it is calculated by the sum of the sub-items scored 0 (incorrect answer) or 1 (correct answer) (Creavin 2016; Folstein 1975). The MMSE will be done only in participants 65 to 74 years of age, inclusive.

8.3.10. Physician Withdrawal Checklist, 20-item (PWC-20)

Potential withdrawal symptoms will be assessed by the PWC-20 according to the SoA.

The PWC-20 is a simple and accurate method used to assess potential withdrawal symptoms following cessation of treatment. The PWC-20 is a reliable and sensitive instrument for the assessment of discontinuation symptoms (Rickels 2008).

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

Adverse events, including AESIs, will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on AEs, SAEs, and PQCs can be found in Section 10.4.

This study allows the use of locally approved (including emergency use-authorized [or country/territory specific equivalent emergency use approved]) COVID-19 vaccines. All AEs, including those following vaccination, should be included in the source and entered in the eCRF. See Section 10.7 for further details regarding COVID-19.

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

All Adverse Events

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

Serious Adverse Events

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

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

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

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

8.4.2. Method of Detecting Adverse Events and Serious Adverse Events

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

Solicited Adverse Events

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

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

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

8.4.4. Pregnancy

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

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

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

8.4.5. Cardiovascular and Death Events

Not applicable

8.4.6. Adverse Events of Special Interest

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

- CCI [REDACTED]
- CCI [REDACTED]

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

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

8.5. Objective Behavior and Physical Measurements (Optional)

Objective Behavior and Physical Measurements will only be administered where applicable and/or permitted per local regulations.

Objective Behavior and Physical Measurements, including CCI [REDACTED] will be performed as optional assessments. In addition, the CCI [REDACTED]

8.5.1.**CCI**

[REDACTED]

8.5.2.**CCI**

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

8.5.3.**CCI**

[REDACTED]

[REDACTED]

CCI

8.6. Biomarkers

Blood samples will be collected during the OL Treatment Phase to evaluate the biomarker status over time during treatment in individuals with diagnostic biosignatures identified at baseline in Studies MDD3001 and MDD3002 and to explore genetic and other factors that may influence the efficacy, pharmacodynamics, safety, or tolerability of aticaprant during long-term treatment. 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. Biomarker samples will be collected in the morning under fasting conditions.

8.7. Immunogenicity Assessments

Not applicable.

8.8. Pharmacogenomic RNA Assessments

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

With participant's consent, blood sample collection per the SoA will be performed to allow for the potential identification of transcriptional changes that may influence the safety, efficacy, or tolerability of aticaprant and to identify transcriptional changes associated with MDD and anhedonia. The RNA will be collected pre- and post-treatment and allow examination of changes in gene transcription related to administration of aticaprant and/or changes in other biomarkers collected during the study.

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

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

may occur during and after completion of the study. The analyses will be described in detail in a dedicated analysis plan.

8.10. Ongoing Participant Review

Adverse events and concomitant medication will be recorded at each visit, including the remote contact visit. The participant will also complete a diary for current antidepressant use at each visit.

8.11. Medical Resource Utilization and Health Economics

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Not Applicable

9.2. Sample Size Determination

Based on the targeted enrollment in the 2 short-term efficacy studies it is anticipated that approximately 715 participants enrolled in the ROW (ie, countries/territories other than China and Japan [if participating]) from these studies will participate in this long-term safety study. Assuming that 50% of the participants will complete 6 months and 33% will complete 12 months of aticaprant exposure, this sample size will meet the ICH E1 guidance requirement of achieving at least 300 participants who have received treatment with aticaprant for 6 months and at least 100 participants for 12 months. It is anticipated that approximately 80 participants from China will participate in the study. In the event Japan participates in the study, approximately 45 participants will be enrolled in this country/territory. Therefore, a total of approximately 840 participants is expected to roll over from the short-term efficacy studies. Additionally, participants may be enrolled directly into the study to meet the target of achieving the required number of participants with 6 months and 1 year of exposure to aticaprant.

9.3. Participant Analysis Sets

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

Analysis Sets	Description
All Participants	All participants who sign the ICF
Safety Analysis Set	All participants (adults and elderly) who received at least 1 dose of study intervention

The analysis of safety data will be performed on the safety analysis set. The analyses of efficacy endpoints along with the corresponding analysis sets will be specified in the Statistical Analysis Plan (SAP). The elderly participants will be summarized separately for selected safety and efficacy analyses which will be detailed further in the SAP.

9.4. Statistical Analyses

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

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

The data will be presented by treatment sequence, namely: placebo/aticaprant 10 mg, aticaprant 10 mg/aticaprant 10 mg for transferred-entry participants (depending on the study intervention group in the short-term efficacy studies), and no DB/aticaprant 10 mg for direct-entry participants. Additionally, a total aticaprant group will be presented.

Two baselines are defined for this study. Baseline (DB/OL) is defined as the last assessment taken on or prior to the first dose of study intervention including the short-term studies for transfer-entry participants. Baseline (OL) is defined as the assessment taken on or prior to the first dose of study intervention in the OL study. Further details on the baseline assessment used for specific summaries will be specified in the SAP.

9.4.1. Safety Analyses

9.4.1.1. Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent AEs (TEAEs) will be included in the analysis.

Treatment-emergent AEs are AEs with onset during the OL phase, or AEs that are a consequence of a pre-existing condition that has worsened since baseline. For each TEAE and AESI (see Section 8.4.6), the percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment sequence.

Serious adverse events will be summarized separately.

Adverse events 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.

9.4.1.2. Vital Sign Measurements

Descriptive statistics of body weight, temperature, pulse/heart rate, respiratory rate, pulse oximetry and blood pressure (systolic and diastolic) values and changes from baseline will be summarized

at each scheduled time point by treatment sequence. Changes in body weight and BMI will be summarized descriptively. Any treatment-emergent abnormalities will be listed.

9.4.1.3. C-SSRS

Suicidal ideation and suicidal behavior based on the C-SSRS will be summarized in incidence and shift tables by treatment sequence.

9.4.1.4. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. 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 by treatment sequence.

The proportion of participants with markedly abnormal results will be presented for each analyte.

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

9.4.1.5. Electrocardiogram Data

The effects on 12-lead 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.

Descriptive statistics of QTc intervals and changes from baseline will be summarized at each scheduled time point by treatment sequence. 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 12-lead ECG findings will be presented. 12-lead ECG data will be summarized by each parameter. Proportion of participants with abnormal 12-lead ECG will be presented.

9.4.1.6. ASEX

Effects of sexual functioning based on the ASEX scale will be summarized by treatment sequence.

9.4.1.7. PWC-20

Withdrawal symptoms based on the PWC-20 will be tabulated by treatment sequence.

9.4.2. Efficacy Analyses

Depression symptoms using the MADRS as well as a patient-reported outcome (PHQ-9), anhedonia symptoms using CCI [REDACTED]

[REDACTED]
global change in severity (CGI-S) as well as CCI [REDACTED] and measurements of SHAPS will be summarized descriptively at each scheduled visit by treatment

sequence using observed data. The proportion of participants who responded and remitted based on the MADRS total score will be provided over time.

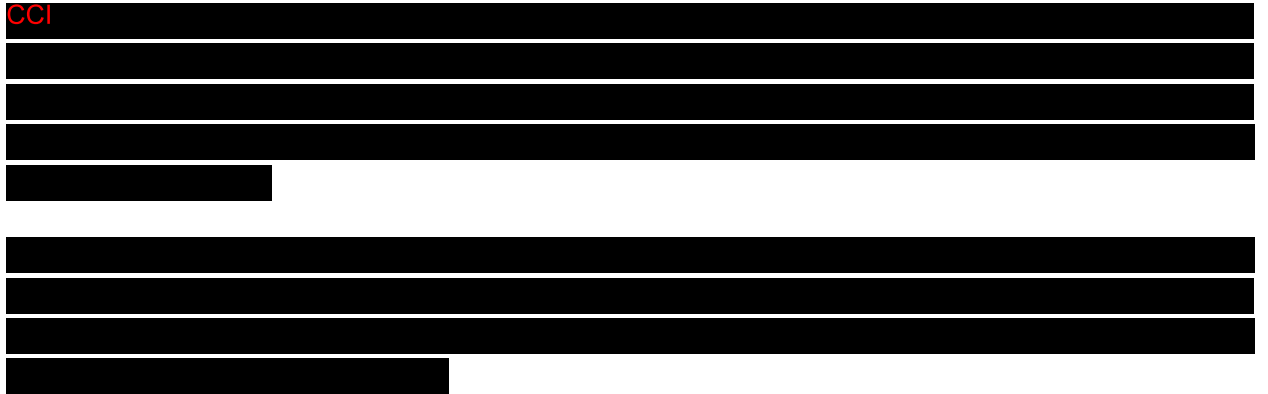
9.4.3. Biomarker Analyses

Biomarker Analyses

The biomarker status over time during OL treatment will be analyzed in individuals with diagnostic biosignatures identified at baseline in Studies MDD3001 and MDD3002.

Digital Biomarker Analyses

CCI

The following content is redacted with black bars: a block of approximately 5 lines of text, followed by a block of approximately 4 lines of text.

9.4.4. Immunogenicity Analyses

Not applicable for this study.

9.4.5. Exploratory Biomarker Analyses

The exploratory RNA, serum, plasma biomarkers will be tabulated. Results may be presented in a separate biomarker report.

9.4.6. RNA Analyses

RNA samples will be used for research related to aticaprant. They may also be used to develop tests/assays related to aticaprant.

Results will be presented in a separate report.

9.5. Interim Analysis

An interim lock of the database is planned once 300 participants have been exposed to aticaprant for 6 months and 100 participants for 1 year in study sites from countries/territories other than China and Japan (if participating) in order to support filing in the ROW. If necessary, other interim lock(s) may be implemented once all the participants in China and/or Japan have completed at least 6 months of study participation depending on the requirement by the respective health authorities.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

AE	adverse event
ADL	activities of daily living
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANH+	with moderate-to-severe anhedonia
ANH-	without moderate-to-severe anhedonia
AP	alkaline phosphatase
API	active pharmaceutical ingredient
ASEX	Arizona Sexual Experiences Scale
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BMI	body mass index
CGI-S	Clinical Global Impression - Severity
CRF	case report form(s) (paper or electronic as appropriate for this study)
C-SSRS	Columbia Suicidality Severity Rating Scale
CSR	clinical study report
CCI	
CCI	
DB	double-blind
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th Edition
eDC	electronic data capture
EOT	End-of-treatment
CCI	
EW	Early Withdrawal
FOIA	Freedom of Information Act
FT ₄	free thyroxine
CCI	
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c / glycated hemoglobin
HDRS-17	17-item Hamilton Depression Rating Scale
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IWRS	interactive web response system
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD ANH+	MDD with moderate-to-severe anhedonia (ANH+)
MDD ANH-	MDD without moderate-to-severe anhedonia (ANH-)
MDD3001	67953964MDD3001 (study number)
MDD3002	67953964MDD3002 (study number)
MDD3003	67953964MDD3003 (study number)
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
MMSE	Mini Mental State Examination
PCP	phencyclidine
PD	pharmacodynamic(s)
CCI	
PHQ-9	Patient Health Questionnaire, 9-item
PRO	Patient-Reported Outcome(s) (paper or electronic as appropriate for this study)
CCI	
CCI	
PWC-20	Physician Withdrawal Checklist, 20-item
CCI	

CCI	
ROW	rest of the world
SAP	Statistical Analysis Plan
SCID-CT	Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version
SHAPS	Snaith-Hamilton Pleasure Scale
SIGH-D	The Structured Interview Guide for the Hamilton Depression Scale
SIQA	Site Independent Qualification Assessment
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t _{max}	time to maximum drug concentration
TSH	thyroid-stimulating hormone
CCI	
ULN	upper limit of normal
CCI	

Definitions of Terms

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

10.2. Appendix 2: Clinical Laboratory Tests

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

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

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count	<u>RBC Indices:</u>	<u>White Blood Cell (WBC) count with Differential:</u>
	Red blood cell count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit	% Reticulocytes	Monocytes
			Eosinophils
			Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. An RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
	Note: An optional/ad-hoc assessment of INR will be performed by the central laboratory in case of liver function parameters elevation.		
Clinical Chemistry	Sodium	Total bilirubin and Direct bilirubin	
	Potassium	Alkaline phosphatase (AP)	
	Chloride	Creatine phosphokinase (CPK)	
	Bicarbonate	Uric acid	
	Blood urea nitrogen (BUN)	Calcium	
	Creatinine	Phosphate	
	Glucose (in fasting condition when possible)	Albumin	
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic	Total protein	
	Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic	Cholesterol:	
	Gamma-glutamyltransferase (GGT)	• Total cholesterol	
		• LDL-cholesterol	
		• HDL-cholesterol	
		Triglycerides	
		Magnesium	
	Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.6.		
	ALT or AST elevations >5 x ULN at least twice over a 2-week period.		
	A possible Hy's Law Case is defined by the occurrence of ALT /AST ≥3 x ULN, ALP <2 x ULN together with Tbili ≥2 x ULN or INR >1.5 (if measured).		

Laboratory Assessments	Parameters	
Routine Urinalysis	<u>Dipstick</u> Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	<u>Sediment (if initial result is abnormal)</u> Red blood cells White blood cells Epithelial cells Crystals Casts 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, or During Treatment)	• Serum or Urine Pregnancy Testing for female participant of childbearing potential only. • Note: a serum pregnancy test must be performed at screening for direct-entry participants, and urine pregnancy tests must be performed as indicated in the SoA to establish absence of pregnancy. Additional serum and urine pregnancy tests may be conducted as needed per the investigator's judgment. • Urine drug test for drugs of abuse (eg, opiates [including methadone], cocaine, amphetamines, methamphetamines, cannabinoids, cannabidiol [CBD], phencyclidine [PCP], barbiturates, or 3,4-methylenedioxymethamphetamine [MDMA]). Urine drug tests will be done by the site at screening, at baseline, and as needed per the investigator's judgment. • In some countries a urine or blood sample may be collected as an optional way to assess compliance with current antidepressant medications. • Thyroid-stimulating hormone (TSH) (screening only) for any participant (regardless of thyroid history), if the TSH value is out of range or for participants with known hypothyroidism who have been on stable treatment for at least 3 months prior to screening, a free thyroxine (FT₄) will be conducted. If the FT₄ 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, FT₄ should be performed whenever the TSH is performed. • Follicle stimulating hormone (FSH) (female participants only) at screening only if required for documentation that a female participant is not of childbearing potential, see Inclusion Criterion 16). • Hemoglobin A1c (HbA1c). • Alcohol breath test (at screening, at baseline, and as needed per the investigator's judgment).	

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

10.3.1. Regulatory and Ethical Considerations

Investigator Responsibilities

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

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

Protocol Clarification Communications

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

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

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

Protocol Amendments

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

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

on an appropriate course of action. The data recorded in the eCRF 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 Pre-study Documentation

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

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

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

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

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

Independent Ethics Committee or Institutional Review Board

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

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

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

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

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

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

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

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

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

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

Country/Territory Selection

This study will only be conducted in those countries/territories where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.4.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.4.

10.3.2. Financial Disclosure

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

Refer to Required Pre-study Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

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

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

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

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

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

10.3.4. Data Protection

Privacy of Personal Data

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

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

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

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

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

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

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

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

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

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section [7.2.2](#)).

10.3.6. Committees Structure

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

10.3.7. Publication Policy/Dissemination of Clinical Study Data

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

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

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

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

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

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

Registration of Clinical Studies and Disclosure of Results

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

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

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

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

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

10.3.9. Case Report Form Completion

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

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

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

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

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

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

10.3.10. Source Documents

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

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

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

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

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

- Height and weight

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

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

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

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

10.3.11. Monitoring

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

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor may compare the data entered into the eCRF 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 eCRF are known to the sponsor and study site personnel and are accessible for verification by the sponsor study site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study site personnel.

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

suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

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

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

10.3.12. On-Site Audits

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

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

10.3.13. Record Retention

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

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

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new

custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

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

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

10.4.1. Adverse Event Definitions and Classifications

Adverse Event

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

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

Note: The sponsor collects AEs starting with the signing of the ICF (refer to All Adverse Events under Section 8.4.1, 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 current 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).

10.4.2. Attribution Definitions

Assessment of Causality

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

Related

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

Not Related

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

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

10.4.3. Severity Criteria

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

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

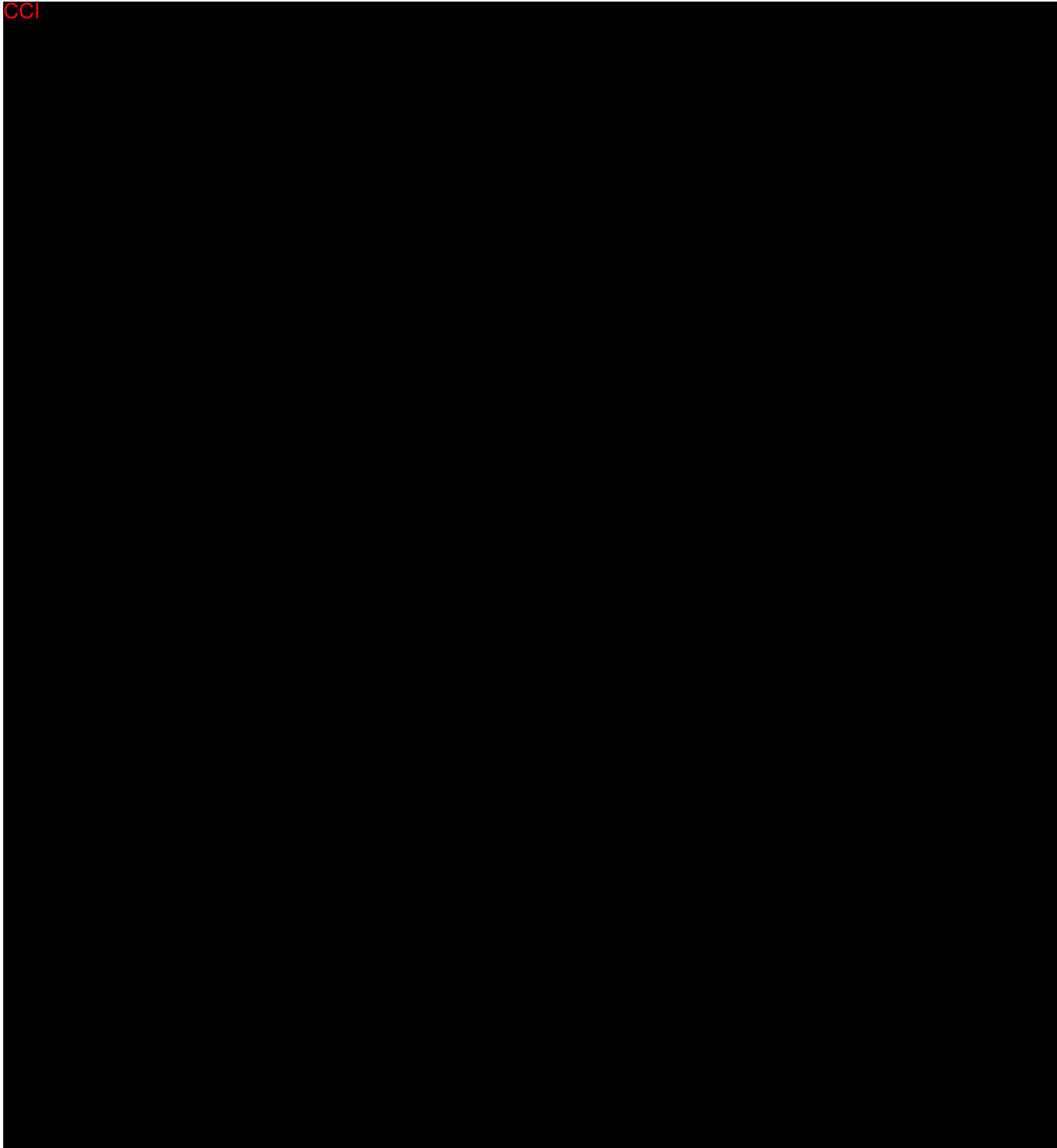
Moderate: Sufficient discomfort is present to cause interference with normal activity.

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

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

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

CCI



10.4.4. Special Reporting Situations

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

- Overdose of a sponsor study intervention

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

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

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF 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 eCRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered SAEs. Any AE that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.
- For convenience the investigator may choose to hospitalize the participant for the duration of the intervention period.

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

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

10.4.6. Product Quality Complaint Handling

Definition

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

Procedures

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

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

10.4.7. Contacting Sponsor Regarding Safety, Including Product Quality

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

10.5. Appendix 5: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.4.4, and Section 10.4.

Definitions

Female Participant of Childbearing Potential

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

Female Participant Not of Childbearing Potential

- **premenarchal**

A premenarchal state is one in which menarche has not yet occurred.

- **postmenopausal**

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

If there is a question about menopausal status in female participants on HRT, the female participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.

- **permanently sterile (for the purpose of this study)**

- Permanent sterilization methods include hysterectomy, or bilateral salpingectomy, or bilateral oophorectomy.
- Has congenital abnormalities resulting in sterility.

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

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

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

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

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES^a ALLOWED FOR MALE OR FEMALE PARTICIPANTS DURING THE STUDY INCLUDE:
USER INDEPENDENT Highly Effective Methods That Are User Independent <i>Failure rate of <1% per year when used consistently and correctly.</i>
• 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 (<i>vasectomized or due to medical cause</i>) <i>(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.)</i>
USER DEPENDENT Highly Effective Methods That Are User Dependent <i>Failure rate of <1% per year when used consistently and correctly.</i>
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable • Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable • Sexual abstinence <i>(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.)</i>
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of $\geq 1\%$ per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action. • Male or female condom with or without spermicide^b • Cap, diaphragm, or sponge with spermicide • A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)^b • Periodic abstinence (calendar, symptothermal, post-ovulation methods) • Withdrawal (coitus-interruptus) • Spermicides alone • Lactational amenorrhea method (LAM)

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

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

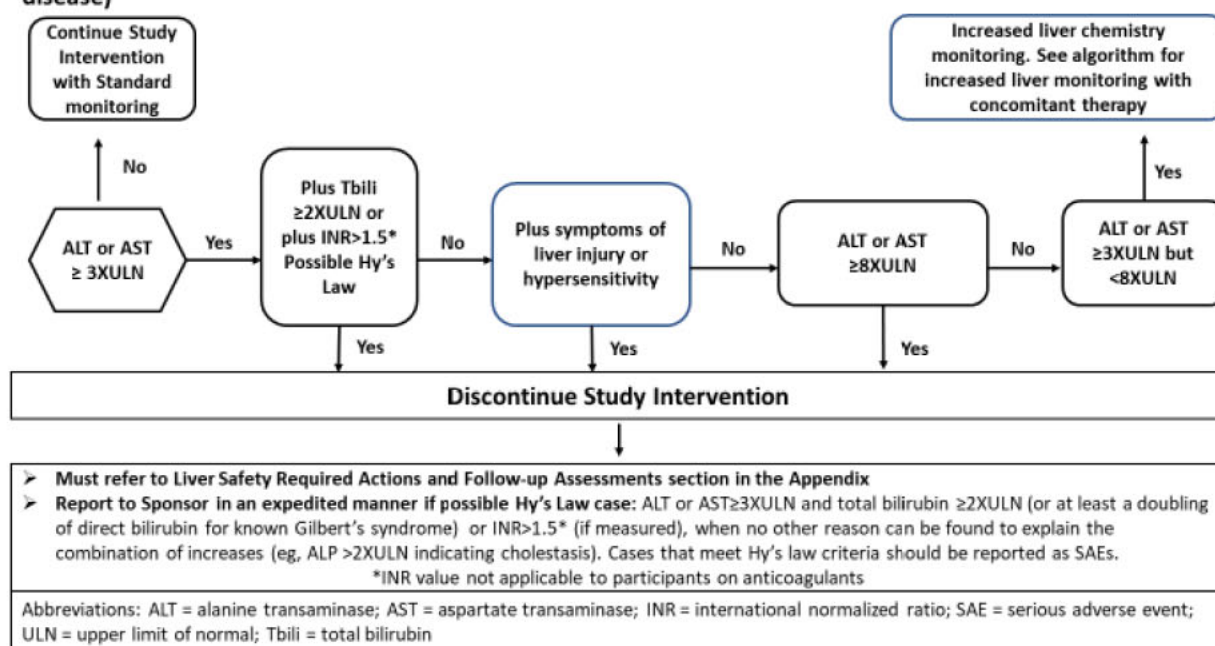
10.6.1. Stopping Algorithm

10.6.1.1. ALT or AST

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

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

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



The following definition of patterns of Drug Induced Liver Injury (DILI) is used when directing the work-up for potential DILI based on elevations of common liver tests (LT):

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

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

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

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

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

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

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

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

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

A liver biopsy may be considered:

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

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

10.6.2. Follow-up Assessments

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

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

10.7. Appendix 7: Study Conduct During a Natural Disaster/Major Disruption/Pandemic

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

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

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

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

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

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

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

10.7.2. Guidance Specific to this Protocol

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

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

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

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

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

Screening Phase (For Direct-entry Participants Only)

The following recommendations apply to those sites within regions where there is a high localized rate of COVID-19 infection with sites temporary closed

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

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

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

Study Intervention

In the event that it is not feasible for the participant to be assessed and receive study intervention at the study site (eg, due to temporary site closure), study intervention may be delivered to the

participant's home. If this is not feasible the participant may discontinue after consultation with the sponsor's medical monitor.

Study-related Procedures

- Rating scales / safety assessments including AEs can continue to be assessed and collected remotely via video teleconferencing (MADRS) or phone (other assessments). Every effort should be made to complete the MADRS assessments via video teleconferencing and within the scheduled timeframe; if this cannot occur, the sponsor's medical monitor or delegate should be contacted for direction.
- Missed/out-of-window visits or individual assessments should be documented with "COVID-19-related" in the comment section of the eCRF.
- It is recommended that close contact be maintained with participants and remote contact arranged consistent with the participant's regularly scheduled visit interval.

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

Laboratory Assessments

If laboratory samples cannot be collected by Covance/central laboratory, sample collection and analysis can be performed using the site's local laboratory at the discretion of the investigator. Local laboratory results will not be collected in the electronic data capture (eDC). Only abnormal laboratory values should be reported as (S)AEs.

- If the investigator does not feel laboratory assessments are required at this time, and participant(s) want to avoid any risk to COVID-19 exposure, this rationale should be documented in the source documents.

Exposure to COVID-19

- If a participant develops COVID-19 infection (or suspected) during the Screening or OL Treatment Phases, the investigator should contact the sponsor's medical monitor to discuss the best course of action based on individual symptoms/ participant setting and risk benefit relationship.
- If a participant develops COVID-19 infection (or suspected) during the Follow-up Phase, the investigator should contact the sponsor's medical monitor and assessments should be completed remotely.
- Every effort should be made to adhere to protocol-specified study intervention dosing schedule and assessments. If administration of aticaprant was interrupted, it may be resumed when safe to do so as determined by the investigator or treating physician in consultation with the sponsor.

Data Collection

- For clinician-completed (MADRS, C-SSRS, CGI-S) scale assessments conducted by a telephone or video contact, the data should be entered directly onto the paper assessment. Ensure that the correct date is present on the assessment form in the eCRF.

- For patient-completed assessments, the CCI and PHQ-9 should be prioritized and collected via the eCOA device.
- Missed doses should be documented in the eCRF in accordance with the eCRF completion guidelines.
- For missed doses, enter a logline with 0 as a number of taken tablets to document the missed dose and a “COVID-19 related” comment entered on the Comments form.
- All COVID-19-related deviations from the main study protocol will be documented according to the eCRF completion guidelines.
- A mitigation plan has been created to address the impact of the COVID-19 global pandemic on the completion of in-person COA assessments.

Statistical Analysis

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

10.8. Appendix 8: Prohibited Concomitant Therapies

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

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

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

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
Attention deficit hyperactivity disorder (ADHD) medications (eg, atomoxetine, guanfacine)	N	N	See also "Psychostimulants" row.	CCI [REDACTED]
Agomelatine	N	N		
Amantadine	N	N		
Amitifadine	N	N		
Antibiotics: Macrolides	N	N		
Antibiotics: Nafcillin	N	N		
Antibiotics: Quinolones	N	N		
Anorexiant (eg, phentermine, phendimetrazine)	N	N		
Anticholinesterase inhibitors	N	N		Participant population is excluded
Anticonvulsants	N	Y	- Participants with uncontrolled (current or past 6 months) seizures are excluded. - Anticonvulsants with strong CCI [REDACTED] and/or CCI [REDACTED] induction potential (eg, CCI [REDACTED]) are excluded. - Others with CCI [REDACTED] and CC [REDACTED] inhibition potential, consult with medical monitor before use. - Use as adjunctive treatment for major depressive disorder (MDD) is prohibited.	CCI [REDACTED]

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
Antidepressants and medications used for treatment of depression (<i>other than the specific antidepressant monotherapies listed in inclusion criteria of the protocol</i>)	N	N	- Only one of the oral antidepressant treatment options listed in Section Inclusion Criteria is permitted. - If a participant is taking a monoamine oxidase inhibitor (MAOI) during the Screening Phase, there must be a minimum washout interval of 2 weeks prior to the first dose of study intervention. - Even if used for other indications (eg, trazodone for sleep), the use of any medication (except the SSRI/SNRI monotherapy options listed in protocol) is not permitted during the treatment phase.	CCI
Antifungals	N	N	Topical antifungals (like terbinafine) are allowed on a case-by-case assessment in consultation with sponsor's medical monitor.	
Antipsychotics	N	N		
Antivirals: non-nucleoside reverse transcriptase inhibitor (NNRTI)	N	N		
Antivirals: Protease inhibitors	N	N		
Appetite suppressants	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	Prohibited within 12 hours prior to CCI completion.	
Benzotropine	Y	N		
Bosentan	N	N		
Buspirone	N	N		

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
Chloral hydrate, melatonin, valerian	N	N		CCI
Clonidine	N	Y	Continuous use for blood pressure control is allowed.	
Conivaptan	N	N		
Corticosteroids	Y	N	Inhaled, intranasal, topical, and ophthalmic steroids are allowed. Intermittent IM/IV corticosteroids are permitted (chronic use prohibited). Episodic or continuous oral use can be discussed on a case-by-case basis with sponsor's medical monitor.	
Crizotinib	N	N		
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		
Monoamino-oxidase inhibitors (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	N	N		
Reserpine	N	N		
Scopolamine	N	N		

Drug Class	Episodic Use (PRN)	Continuous Use	Comments	Reason for Prohibition
St. John's Wort	N	N		CCI
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 the treatment phase.	
Trazodone	N	N	Not allowed even if used for other indications (eg, for sleep).	

Abbreviations: ADHD: attention deficit hyperactivity disorder; IM: intramuscular; IV: intravenous; MAOI: monoamine oxidase inhibitor; N: Prohibited; NNRTI: non-nucleoside reverse transcriptase inhibitor; PD: pharmacodynamics; PK: pharmacokinetics; PO: oral; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; T3: tri-iodothyronine; 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.

10.9. Appendix 9: Administration of a Patient-Reported Outcome (PRO) at Scheduled Visits

The following guidance will be followed to administer a PRO:

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

10.10. Appendix 10: Protocol Amendment History

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

Amendment 1 (08 September 2022)

Overall Rationale for the Amendment:

Updates are made based on feedback received from interactions with health authorities, key opinion leaders in the MDD field and potential investigational sites involved in the study feasibility, to ensure alignment across the program and to improve patient selection. Minor changes are made throughout the protocol for compliance with updated protocol template text, for clarification, and to correct errors.

The changes made to the Clinical Protocol 67953964MDD3003 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
Synopsis	Added a brief description aligned with the main text: “ Aticaprant (JNJ-67953964) is a once daily, highly selective KOR antagonist, with demonstrated selectivity over mu opioid receptor (MOR) and delta opioid receptor (DOR). ”	To improve flow of the synopsis.
Synopsis Benefit-Risk Assessment	Added Benefit-Risk Assessment section to Synopsis.	To align with the most current protocol template.
3. Objectives and Endpoints	Added an additional set of exploratory objectives and endpoints for participant subgroups: adult participants with MDD ANH-, and all MDD participants. Minor updates to wording throughout.	To capture similar objectives and endpoints for MDD ANH- and all MDD (exploratory) as in the secondary objectives. To align with other Phase 3 studies.
Synopsis Number of Participants; Synopsis Sample Size Calculation; 1.2. Schema; 4.2.1. Study Population; 9.2. Sample Size Determination	Updated information on number of participants with clarifications on participant number enrolled in the ROW, China and Japan.	To reflect the number of participants rolling over from 2 2-arm short term studies.
Synopsis Overall Design; 4.1.2. Screening Phase; 5.1.2. Direct-entry Participants	Updated Inclusion Criterion 7 on number of inadequate treatments (carried though to other relevant sections, as noted): “Have had an inadequate response to at least 1 but no more than ~~2~~ 3 antidepressants (see in the inclusion criterion ~~8~~ below), administered at an adequate dose (therapeutic dose per MGH ATRQ) and duration (at least 6 weeks) in the current episode of depression. ~~The current antidepressant cannot be the first antidepressant treatment for the first lifetime episode of depression.~~ ” Updated definition of inadequate response to current antidepressant: “An inadequate response is defined as <50% reduction but	Based on feedback received from clinicians-opinion leaders and practicing psychiatrists the maximum number of historical inadequate responses to current antidepressant treatment is updated to reflect clinical reality and improve patient selection. The change further aligns with respective criteria for the population enrolled in prior programs of already approved adjunctive agents. Updates are made in the wording of the criteria and information on the clinical

Section Number and Name	Description of Change	Brief Rationale
	with some improvement during the current antidepressant trial (ie, there may be some minor to moderate symptomatic improvement $\geq 0\%$ since the initiation of the antidepressant treatment, but some of the initial symptoms are still present, troubling to the participant and overall good tolerability affecting behavior and function) as assessed by the MGH ATRQ. Note: Medical/pharmacy/prescription records or records of conversation with the treating physician, or other equivalent documents can be used to verify the adequacy of the current antidepressant trial.” Removed note regarding participants with no response/lack of clinically meaningful improvement: ~~“Note: Participants with no improvement on the current SSRI/SNRI should not be enrolled in the study. If the participant has received 2 SSRI/SNRI treatments of sufficient dose and duration in the current episode, and has shown $\leq 25\%$ improvement to both, then the participant would not qualify based on exclusion criterion 6.”~~	context to the definition of “inadequate response” is added to provide clarity to the sites; ensure alignment in assessing this criterion and improve participant selection.
Synopsis Overall Design; 1.2. Schema; 4.1.1. Study Intervention(s); 4.1.2. Screening Phase; 4.1.3. Open-label Treatment Phase; 6.1. Study Intervention(s) Administered; 6.3. Measures to Minimize Bias: Randomization and Blinding; 6.8.1. Current (SSRI/SNRI) Antidepressant Therapy	Updated wording on the current antidepressant use throughout (example from 4.1.1): “All participants should ~~will~~ continue to take their OL current SSRI/SNRI antidepressant throughout the entire study treatment phase (see Section 4.1.3 for a list of antidepressants), unless significant tolerability issue occurs, in which case the oral SSRI/SNRI antidepressant may be discontinued and if appropriate, switched to a new SSRI/SNRI antidepressant (from those listed in Section 4.1.3) ~~after discussion with sponsor’s study responsible physician/scientist or designee. Only one switch of SSRI/SNRI may be made during the OL Treatment Phase.~~ The proposed change and the reason must be discussed with sponsor’s study responsible physician/scientist or designee and documented in the eCRF.”	To provide clarification on the current antidepressant therapy use, possibility to switch, and to align throughout the protocol.
Synopsis Overall Design; 1.3. Schedule of Activities; 4.1.4. Follow-up/End of Study Visit	Indicated that the Follow-up Visit (ie, Visit 3.1) must indicate 7-14 days after Visit 2.14 (EOT/EW), instead of 7-14 days after last dose of study intervention.	Editorial change to align the SoA with the protocol’s instructions on timing of the Follow-up Visit after End-of-treatment/Early Withdrawal Visit.
Synopsis Overall Design, Statistical Methods; 4.1. Overall Design,	Removed text related to assessment of withdrawal symptoms using the Physician’s Withdrawal Checklist (PWC-20).	Assessment of withdrawal symptoms using the PWC-20 is not performed in this study.

Section Number and Name	Description of Change	Brief Rationale
Synopsis Statistical Methods; 9.4. Statistical Analyses	Added text to note that the data will be summarized by treatment sequence.	Added language for clarity.
1.2. Schema	Added in footnote: “Screening Phase applies only to direct-entry participants.”	Editorial changes: to improve understanding which visit/procedures apply to direct-entry participants.
1.3. Schedule of Activities	Added assessments on Visits 1.1 and 1.2: TSH/FT ₄ ; HbA1c, and Lipid panel (fasting), respectively.	To provide a complete set of assessments required for direct-entry participants.
1.3. Schedule of Activities	The following assessments at Visit 3.1 (Follow-up) were removed: hematology, chemistry; urinalysis; and menstrual cycle tracking.	Assessments removed to reduce the number of assessments and burden during Follow-up Visit.
1.3. Schedule of Activities	Added footnote “v”: “For participants that require translation of the CCI [REDACTED] into their local language, the collection of the CCI [REDACTED] is optional until the final, approved translation is available.”	Footnote included to explain that flexibility is allowed for the completion of the PRO based on translation available in a particular country.
1.3. Schedule of Activities	Added footnote “w”: “If blood sampling or vital sign measurement is scheduled for the same time point as 12-lead ECG recording, the procedures are recommended to be performed in the following order: 12-lead ECG, vital signs, blood draw.”	Editorial change to improve understanding of expected procedure sequences during study visits.
1.3. Schedule of Activities	Updated footnote “g”: “A urine ~~and/or~~ blood sample will be collected and sent to the central laboratory to assess compliance with current antidepressant medications. ~~If urine and/or blood test is negative, one retest may be performed at the discretion of the investigator. With a negative test, Additionally,~~ other means of assessing adherence, including confirming prescription records and performing pill counts and prior good compliance with antidepressant medication may be sufficient to demonstrate compliance per investigator’s judgment.”	Editorial change to provide additional clarification on the acceptable methods of assessing participants adherence/compliance to their current antidepressant medication.
1.3. Schedule of Activities	Added footnote “x”: “Not applicable for China.”	To clarify that pharmacogenomics assessment is not applicable to China (country will use the global protocol).
2.3.2. Benefit-Risk Assessment for Study Participation	Added information on direct- and transferred-entry participants.	Editorial edit to provide more clarity on study design.
4.1.2. Screening Phase	Updated text on adequate trial definition: “An adequate trial is defined as an antidepressant treatment for at least 6 weeks on a stable dose at or above the minimum therapeutic dose specified in the MGH ATRQ. This must also apply to the participant’s current antidepressant treatment. The inadequate response must include the participant’s current SSRI/SNRI treatment. ”	To align with Inclusion Criterion 7.

Section Number and Name	Description of Change	Brief Rationale
	Medical/pharmacy/prescription records or records of conversation with the treating physician, or other equivalent documents can be used to verify the adequacy of the current antidepressant trial ~~inadequate treatment status.~~	
4.1.3. Open-label Treatment Phase	Added details on ICF signing for transferred-entry participants.	To clarify the process and timing of ICF for MDD3003 for transferred-entry participants.
4.2.2. RNA and Biomarker Collection	Updated: “The biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately targeted individualized therapies.”	Editorial edit to clarify the wording.
4.2.4. Study-Specific Ethical Design Considerations; 8. Study Assessments and Procedures	Updated blood volume to be collected from each participant.	Blood volume collected in study updated following removal of sampling for hematology and chemistry at Visit 3.1, and to ensure that sampling at Visits 1.1, 1.2, 2.4, 2.7, 2.10, and 2.13 is captured.
5.1.2. Direct-entry Participants	Revised Criterion 8: “Is currently receiving and tolerating well any one of the following SSRI or SNRI for depressive symptoms at screening, in any formulation and available in the participating country/territory: citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, milnacipran, levomilnacipran, paroxetine, sertraline, venlafaxine, desvenlafaxine at a stable dose (at a therapeutic dose level per MGH ATRQ) for at least 6 weeks and with some minor to moderate symptomatic improvement (>25%). The current antidepressant cannot be the first antidepressant treatment for the first lifetime episode of depression. ”	Clarification made to improve understanding regarding the antidepressant (SSRI or SNRI) the participant is currently taking and will be continued in the treatment phase. Last sentence is moved from Inclusion Criterion 5 as the information pertains to the current antidepressant.
5.2.2. Direct-entry Participants	Updated Exclusion Criterion 6 on exclusion of participants with non-response to the current SSRI/SNRI: ~~“Has a history of treatment resistant MDD, defined as Participant has a lack of response to 2 or more adequate antidepressant treatments in the current episode, as indicated by no or minimal clinically meaningful improvement (≤25% improvement) when treated with an antidepressant of adequate dose (per MGH ATRQ) and duration (at least 6 weeks) to the current SSRI/SNRI (ie, the one presumed to be continued in the treatment phase) assessed using the MGH ATRQ.”~~	Update in wording on the exclusion criterion to provide further clarity to the definition of non-response to the current antidepressant treatment and which participants are not eligible for the studies.
5.2.2. Direct-entry Participants	Updated Exclusion Criterion 16 as follows: “Has clinically significant 12-lead ECG abnormalities at the start of the Screening	Editorial update to improve understanding of the exclusion

Section Number and Name	Description of Change	Brief Rationale
	Phase or on Day 1 of the OL Treatment Phase prior to the first aticaprant dose that may jeopardize the participants' safety or the integrity of the study, in the investigator's judgment, defined as ..."	criterion and to align across Phase 3 studies.
5.3. Lifestyle Considerations	Moved restriction regarding alcohol to Section 5.3.1. Meals and Dietary Restrictions. Deleted Section 5.3.2. Caffeine, Alcohol, and Tobacco.	Editorial change to align across Phase 3 studies.
5.3.2. Activity	Modified wording to indicate participants should (not must) "abstain from strenuous exercise..." and "be advised not to donate blood..."	To reduce burden on participant by making the lifestyle considerations related to activities only recommendations.
5.4. Screen Failures	Added text: "When available, the investigator may generate screening and enrollment logs directly from IWRS."	To align with the most current protocol template.
6.1. Study Intervention(s) Administered	Added text: "Non-investigational Medicinal Product/ Auxiliary Medicinal Product ".	To align with the most current protocol template.
6.4. Study Intervention Compliance	Added text: "Missing study intervention doses due to temporary interruption per Section 7.1.4 will not be considered noncompliance."	To clarify that protocol-mandated interruptions of study intervention are not considered as noncompliance.
6.8. Concomitant Therapy	Updated: "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 (for direct-entry participants). This includes non-pharmacological treatments (eg, psychotherapy, transcranial magnetic stimulation [TMS]). Antidepressant pharmacological treatments which are not listed on the MGH ATRQ but were used, or are currently being used, as antidepressant treatment in the current depressive episode ~~will have these medications tapered (if applicable) and discontinued during the Screening Phase, per the local prescribing information or clinical judgment (for a complete list of antidepressant medications, please refer to Section 10.8, for a list of medications used for the treatment of depression to be discontinued during the Screening Phase). Non-listed antidepressants~~ must be recorded in the 'Concomitant Therapy' eCRF. [...] Participants should continue to take their permitted concomitant medications at their regular schedule; however, restrictions as outlined in Section 6.8.2. ~~Also see and~~ Section 10.8 should be taken into account for additional information ~~of the prohibited concomitant medications."~~	To align with the most current protocol template.
7.1. Discontinuation;	Updated text: "AST and/or ALT ~~exceeds~~ >5 x ULN (confirmed by repeat testing). AST	To align with the liver chemistry stopping criteria.

Section Number and Name	Description of Change	Brief Rationale
7.1.2. Liver Chemistry Stopping Criteria	and/or ALT ~~exceeds~~ ≥ 3 x ULN and total bilirubin ~~exceeds~~ ≥ 1.5 ≥ 2 x ULN..."	
7.1.4. Treatment Interruptions, Restart, or Re-Challenge	Updated: "The following guidance should be considered during the study treatment phase for moderate/severe upper GI symptoms suggestive of ulcer or heartburn lasting more than 3 days and with no potential alternative causes according to the clinical judgment: ~~If during the study treatment phase, a participant reports moderate/severe upper gastrointestinal symptoms suggestive of ulcer or heartburn lasting more than 3 days and with no potential alternative cause according to the clinical judgment.~~ The oral study intervention should be interrupted."	To align across Phase 3 studies.
8. Study Assessments and Procedures	Updated to include instructions on completion of PRO assessments when on-site and at home, and added more details on interview with site-based rater.	To align across Phase 3 studies.
8.1.1. Montgomery-Åsberg Depression Rating Scale (MADRS)	Removed text in the following sentence: "The typical recall period for the MADRS is 7 days ~~and will be used for the primary efficacy evaluation.~~ "	MADRS is not the primary efficacy evaluation in this study.
8.1.1. Montgomery-Åsberg Depression Rating Scale (MADRS); 8.5.1. Speech Biomarker Analysis (Optional)	Modified text: " ~~All~~ MADRS assessments ~~will~~ may be video-recorded for the purpose of quality monitoring." Modified text: "In this study, the MADRS physician-patient interview ~~will~~ may be recorded for data quality monitoring."	To provide clarity that a participant has the possibility to opt out of video-recording at an individual visit.
8.2.1. Hamilton Depression Rating Scale (HDRS-17)	Added Williams 1988 reference for SIGH-D and added text on audio recording: "HDRS-17 assessments will be administered by independent remote raters and will be audio-recorded for the purpose of quality monitoring. "	To provide a reference for the scale and clarify that the assessments are audio-recorded.
8.2.4. Site Independent Qualification Assessment (SIQA)	Modified text: " ~~Remote, independent remote~~ psychiatrists/psychologists will perform the qualification assessment for all participants to confirm the validity of a diagnosis of depression, the severity of the depressive symptom and eligibility for the study (Targum 2008) . The interviewer will review participant screening information and conduct a live, remote interview with the participant. This interview will include conducting HDRS-17 during screening , ~~to be performed by the same rater, and will be video recorded for the purpose of quality monitoring.~~ "	To provide a reference for the procedure and clarify that HDRS-17 assessments are not video-recorded.
8.3.1. Physical Examinations	Removed "and waist circumference."	Not measured in this study.
8.3.3. Electrocardiograms	Added: " During screening (for direct-entry participants only), a QT interval corrected according to Fridericia's formula (QTcF): ≥ 450 msec (males); ≥ 470 msec (females) should be obtained. "	To align with the Exclusion Criterion 16 and across Phase 3 studies.

Section Number and Name	Description of Change	Brief Rationale
8.3.4. Clinical Safety Laboratory Assessments, 10.2. Appendix 2: Clinical Laboratory Tests	Revised text regarding FSH as follows: “follicle stimulating hormone (FSH) (female participants only, at screening only if required for documentation that a female participant is not of childbearing potential, see Inclusion Criterion 16 ~~Section 5.1.3~~).”	Revised for consistency with text in Section 8.2.4 and Section 10.2.
8.3.7. Columbia Suicidality Severity Rating Scale (C-SSRS)	Updated heading and description of the C-SSRS.	To align across Phase 3 studies.
8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting	Added language regarding COVID-19 as follows: “All adverse events, including those following vaccination, should be included in the source and entered in the eCRF. See Section 10.7 for further details regarding COVID-19. ”	To align with the most current protocol template.
8.4.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.4.5. Procedures	Wording was updated to: “Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF , which must be completed and reviewed signed by a physician from the study site, and transmitted to the sponsor immediately but no later than within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first. ”	To align with the most current protocol template for studies with safety gateway, and ensure it is also reflected correctly in the appendix.
8.4.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events Throughout the protocol	Updated: “For the purposes of this study the following ~~events will be considered anticipated events. For the purposes of this study, if any of the following are reported as an SAE, these SAEs~~ will be considered anticipated events:...” Updated instances of “country” to “country/ territory ” where applicable.	To align with the most current protocol template.
9.3. Populations for Analysis Sets	Changed the heading of Section 9.3 to “Participant Analysis Sets.” Changed “populations” to “analysis sets” in these sections.	To align with the most current protocol template.
9.4.3. Biomarkers Analyses	Updated description of Digital Biomarkers Analyses.	Adding “de-identified” to add clarity on data handling and ease privacy concerns; to provide further information on the procedure and align across Phase 3 studies.
10.2. Appendix 2: Clinical Laboratory Tests	Updated (re-ordered some classes included previously): “• Urine drug ~~test Screen~~ for drugs of abuse (eg, opiates [including methadone], cocaine, amphetamines/, methamphetamines, cannabinoids, cannabidiol [CBD] , phencyclidine [PCP]), barbiturates, or 3,4 methylenedioxymethamphetamine [MDMA]). Urine drug ~~tests screens~~ will be	To align with Exclusion Criterion 19.

Section Number and Name	Description of Change	Brief Rationale
	done by the site at screening, at baseline, and as needed per the investigator's judgment. [...] Alcohol breath test (at screening, at baseline, and as needed per the investigator's judgment.)”	
10.2. Appendix 2: Clinical Laboratory Tests	Updated statement regarding definition of Hy's Law Case.	To align with the most current protocol template.
10.5. Appendix 5: Contraceptive and Barrier Guidance	Removed footnote 'b' ("Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.") from Examples of Contraceptives table.	To align with the most current protocol template (template update in line with comments from an HA).
10.7.1. Guidance on Study Conduct During the COVID-19 Pandemic (Appendix 7)	Added statement on re-consenting participants.	To clarify the procedure and align with other Phase 3 studies.
10.8. Appendix 8: Prohibited Concomitant Therapies	Text updated: “- Participants with uncontrolled (current or past 6 months) seizures are excluded. - Anticonvulsants with strong CCI and/or CCI induction potential (eg, carbamazepine, phenytoin) are excluded. Others with CCI and CCI inhibition potential, consult with medical monitor before use. - Use as adjunctive treatment for major depressive disorder (MDD) is prohibited. ~~Note: Anticonvulsants used for indications other than seizures may be allowed (e.g., valproate for migraine, pregabalin). Approval for use can be discussed on a case by case basis with the sponsor's medical monitor.~~ Potential PD interaction PK-CCI and CCI induction. ”	List of prohibited therapies updated to align with exclusion of seizures criterion. The prohibition of anticonvulsants was reconsidered based on the fact that only current or history of (6 months) seizures are exclusionary. Given the above update to the exclusion criteria and potential for strong CCI and CCI induction potential with certain anticonvulsants, their exclusion is recommended.
10.8. Appendix 8: Prohibited Concomitant Therapies	Updated test for trazodone, psychostimulants, clonidine.	To improve protocol understanding and clarify the use of certain prohibited therapies.
10.10. Appendix 10: Protocol Amendment History	Added the following text: “ The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents. ”	To direct readers to the Summary of Changes Table.
4.1.2. Screening Phase; 6.8.1. Current (SSRI/SNRI) Antidepressant Therapy	Removed the following text: “If needed (eg, a longer tapering required for prohibited therapies or other circumstances)...” Removed: “The current antidepressant will not be provided by the sponsor ...”	Editorial change to remove duplication.
Throughout the protocol	Revised wording to specify participant's characteristics by sex (not gender), eg, “ ~~women~~ female participants. ”	To align with health authority guidance.

Section Number and Name	Description of Change	Brief Rationale
	Inclusion Criteria 15, 16, 17, and Exclusion Criterion 30 revised to specify participant's characteristics by sex (not gender).	
Throughout the protocol	Updated abbreviation: CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED]	To reflect the name of the questionnaire correctly.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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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	22-Feb-2023 14:47:33 (GMT)	Document Approval