

Janssen Research & Development

Statistical Analysis Plan

**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

**JNJ-67953964 Aticaprant
Amendment 2**

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
10.0	21 Oct 2024 – Amendment 2	Section 5.3.2.2. & 5.3.4.2 add “The above analyses will be conducted for FAS_ANH+ _e.” for PHQ-9 and CGI-S change from baseline	To be consistent with the protocol.
		Minor fixes	
7.0, 8.0, 9.0	9 Aug 2024 – Amendment 2	Minor fixes	
6.0	7 August 2024 - Amendment 2	Section 4, appendix 1: modified definitions of MDD WOANH MS	To clarify.
5.0	1 August 2024 - Amendment 2	Sections 1, 1.1, 4, 5.1. Replaced MDD ANH- with Non-PAP	Non-PAP more accurately reflects the population, i.e., subjects who are not in the primary analysis set.
		Section 4, 6.3. Replaced FAS_ANH- with newly defined non-enriched populations	The FAS_ANH- population will not be analyzed as a separate group as a portion of this population includes participants with moderate-to-severe anhedonia (i.e., SHAPS total score ≥ 32). Hence, replaced the analysis set with the newly defined non-enriched populations.
		Sections 5.1, 5.3. Removed FAS_ANH-	Please see above.
		Section 5.3.2.1 PHQ-9 - Confirmed the definition of remitter based on is PHQ-9 total score is <5	To clarify.
		Section 5.3.2.2. PHQ-9 - Added “ ≥ 2 at baseline” in the PHQ-9 anhedonia-specific item (item 1) summary	
		Section 5.5.1. Extent of Exposure - Modified the definition of 6 months to 26 weeks and 12 months to 52 weeks	To align with defined exposure interval categories.
		Section 5.5.3 Adverse Events - added additional analyses for AESI and AE of clinical interests	To clarify the details of analyses for AESI and AE of clinical interests.
		Section 5.5.4.1. Clinical Laboratory Tests – Further detail added to the criteria of hepatic toxicity	To clarify.
		Section 5.5.4.4. Physician Withdrawal Checklist, 20 item (PWC-20) – added additional analysis of comparison between follow-up to endpoint (OL)	To align with parent study MDD3002.

SAP Version	Approval Date	Change	Rationale
		Section 5.6.4. Subgroups Analyses – modified definitions of subgroups, including age group and number of major depressive episodes.	To better characterize the treatment effect in various sub-groups
		Section 6.3. Appendix 3 Demographics and Baseline Characteristics – modified and added variables definitions	To better characterize the study population
		Throughout the document: Added additional information for clarity	
4.0	26 February 2024 - Amendment 1	Section 1.2 Study Design – updated description.	Made this change based on protocol Amendment 2.
		Section 3 SAMPLE SIZE DETERMINATION – updated sample size determination for enrollment in Japan.	Made this change based on protocol Amendment 2 to clarify that Japan’s participation is optional in the study.
		Section 4 POPULATIONS (ANALYSIS SETS) FOR ANALYSIS – added “All Participants (direct-entry)”, which is defined as all direct-entry participants who sign the informed consent form (ICF), was added.	Added population set definition for specified analyses.
		Section 5.1 General consideration – added definition of baseline (DB/OL) and baseline (OL) in this SAP.	To describe analyses conveniently.
		Section 5.1.2. Visit Windows – Merged the sections by adding some footnotes for definitions in this section including baselines and relative study day. Modified visit windows intervals.	To make the context precisely and this change based on protocol Amendment 2.
		Section 5.4.7. CCI – updated scoring methods.	To be aligned with updated definition cross MDD studies.
		Section 5.5.2. Compliance – modified definition of current antidepressant while on study intervention compliance.	To clarify.
		Section 5.5.1. Extent of Exposure – removed the definition of “Number of doses” and added the definition of “Total dosing days of intervention”, which is defined as the total number of days that study intervention was administered to the participant (excluding days off study intervention).	Modified definitions as participants are required to take the medication once daily.
		Section 5.5.3 Adverse Events-minor modified typos and wordings; add several analyses	To clarify details of AESIs analyses.

SAP Version	Approval Date	Change	Rationale
		for adverse event of special interest.	
		Section 5.5.4.1. Clinical Laboratory Tests – updated criteria related to the analysis of treatment-emergent hepatic toxicity	To be aligned with updated definition cross MDD studies.
		Section 5.5.4.2. Vital Signs and Physical Examination Findings – modified analysis period from each phase to open-label phase.	To clarify analysis period.
		Section 5.5.4.3. Electrocardiogram – add definition of baseline.	To more clarify.
		Section 5.5.4.4.1. Columbia Suicide Severity Rating Scale (C-SSRS) – added some part of definition of C-SSRS.	To be aligned with updated definition cross MDD studies
		Section 5.5.4.4.1. Columbia Suicide Severity Rating Scale (C-SSRS) – updated brief introduction on the concept of C-SSRS; replaced analyses from baseline (OL) by baseline (DB/OL) of C-SSRS.	To clarify the concept and to extend analyses by including transferred DB phase.
		Section 5.5.4.4.2. Arizona Sexual Experiences Scale (ASEX) – added several subgroup analyses (responder status at end of parent study; sex; age group)	To provide more analyses focusing on sexual dysfunction.
		Section 5.5.4.4.3. Menstrual Cycle Tracking – added the definition of length of menstrual cycles at each time category and exposure categories, and removed duration of menses.	To add details and clarify.
		Section 5.5.4.4.4. Physician Withdrawal Checklist, 20 item (PWC-20) – added statement that this will only be analyzed on transferred participants from MDD3002.	To clarify.
1	13 January 2023	Not Applicable	Initial release

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses for study 67953964MDD3003.

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

1.1. Objectives and Endpoints

This is an open-label (OL), long-term, safety and efficacy study of aticaprant as adjunctive therapy in adult and elderly participants with major depressive disorder (MDD).

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)
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
• Symptoms of anhedonia (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	
CCI	

Objectives	Endpoints
CCI	
CCI	

* 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 an adequate dose (at or above the minimum therapeutic per MGH ATRQ) throughout the study.

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.

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.

All eligible participants (transferred- and direct-entry) will receive OL aticaprant treatment at a dose of 10 mg starting on Day 1 (OL Baseline) without breaking the blind from the prior study for the transferred-entry participants. Throughout the study, participants should continue their current SSRI/SNRI antidepressant (at the same dose and taken around the same time of the day as prior to entering the study), 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 below). The proposed change and the reason must be discussed with the 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 one of these allowed antidepressants at an adequate and tolerated dose (ie, monotherapy) during the study. The sponsor will not supply these antidepressant medications.

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 health 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;

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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.

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

2. STATISTICAL HYPOTHESES

There is no formal hypothesis for this safety study.

3. 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 rest of the world (ROW, ie, countries/territories other than China and Japan) 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 Conference 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. It is anticipated that approximately 80 participants from China and Japan 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.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

Analysis Sets	Description
All Participants	All participants who sign the informed consent form (ICF)
All Participants (direct-entry)	All direct-entry participants who sign the informed consent form (ICF)
Full Analysis Set (All) (FAS_All)	All participants (adults and elderly) with MDD ANH+ or non-PAP who received at least 1 dose of study intervention
Full Analysis Set (ANH+) (FAS_ANH+)	All adult participants with MDD ANH+ who received at least 1 dose of study intervention
MDD_WOANH_S Analysis Set	Adult participants with baseline SHAPS total score <32 who take at least 1 dose of study intervention.
MDD_WOANH_MS Analysis Set	Adult participants with baseline SHAPS total score <32 or SCID-CT item 2=No, and MADRS≥25 who take at least 1 dose of study intervention.
Full Analysis Set (elderly ANH+) (FAS_ANH+_e)	All elderly participants with MDD ANH+ who received at least 1 dose of study intervention
Safety Analysis Set	All participants (adults and elderly) who received at least 1 dose of study intervention
Safety Analysis Set (adults)	All adult participants who received at least 1 dose of study intervention
Safety Analysis Set (elderly)	All elderly participants who received at least 1 dose of study intervention
Follow-up Analysis Set	All participants (adults and elderly) who entered the follow-up phase after open-label treatment phase

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Note: Due to Good Clinical Practice (GCP) issues, participants enrolled in site US10108 will be included in the all participants analysis set, but not in the efficacy and safety analysis sets. Patient profiles will be provided for these participants.

If the short-term study in China is ongoing at the time of ROW submission, participants in these countries/territories will be excluded in the summaries and analyses.

5. STATISTICAL ANALYSES**5.1. General Considerations**

The analysis of safety and efficacy data will be performed on the FAS_All analysis set, which includes all participants (adults and elderly) with MDD ANH+ or non-PAP participants who received at least 1 dose of study intervention. Unless specified, the analysis of efficacy data will also be performed on adult MDD ANH+ using FAS_ANH+. Elderly participants will be summarized separately for select safety and efficacy analyses using safety analysis set (elderly) and FAS_ANH+_e analysis sets, respectively. As the non-PAP group also consists of participants with moderate-to-severe anhedonia (i.e, SHAPS total score ≥ 32), exploratory endpoints described in the protocol will not be analyzed for this population.

MDD ANH status will be determined for the direct-entry participants based on the criteria presented in the addendum to the protocol. For the transferred entry participants, the MDD ANH status from their respective parent study will be applied.

For all continuous safety and efficacy variables, descriptive statistics will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Efficacy evaluations will be summarized descriptively at each scheduled visit using observed data, unless otherwise specified.

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.

For some of the analyses described in the document the following two different baselines are used: baseline (DB) for transferred entry participants, and baseline (OL) for direct entry participants. For ease of discussion, the two baselines are jointly referred to as, 'baseline (DB/OL)'.

5.1.1. Analysis Phases**Open-label Treatment Phase**

The analysis reference start date of the OL treatment phase (OL phase start date) is the date of the first dose of the OL aticaprant. The analysis reference end date of the OL treatment phase (OL

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phase end date) is the maximum of the date the last visit in the OL treatment phase and date of completion or early withdrawal from the OL treatment phase.

Follow-up Phase

The analysis reference start date of the follow-up phase (follow-up phase start date) is the day after the reference end date for the open-label treatment phase. The analysis reference end date of the follow-up phase (follow-up phase end date) is the date of the maximum of the date of the last visit in the follow-up phase, and trial disposition.

5.1.2. Visit Windows

As participants do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to analysis visits. Listed below are the visit windows and the target days for each visit. The reference day is Study Day 1. If a participant has 2 or more actual visits in 1 visit window, the visit closest to the target day will be used as the protocol visit for that visit window. The other additional visit(s) will not be used in the summaries or analyses, but they can be used for determination of clinically important endpoints. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used.

All assignments will be made in chronological order. Once a visit date is assigned to a visit window, it will no longer be used for a later time point except for the endpoint. Listed below (Table 2) are the analysis visit windows and the target days for each visit defined in the protocol.

Table 2: Visit Windows

Parameter	Analysis Phase	Scheduled Visit Number	Time Interval	Time Interval (Day)*	Target Time Point (Day)
Vital signs, C-SSRS	SCR ^a	1.1	Screening	-30 to -2	
		1.2	Screening	-30 to -2	
	OL	x	Baseline (DB) ^b	<=1 [§]	
		2.1	Baseline (OL) ^c	<=1	1
		2.2	Week 4	2 to 42	29
		2.3	Week 8	43 to 70	57
		2.4	Week 12	71 to 98	85
		2.5	Week 16	99 to 126	113
		2.6	Week 20	127 to 154	141
		2.7	Week 24	155 to 182	169
		2.8	Week 28	183 to 210	197
		2.9	Week 32	211 to 238	225
		2.10	Week 36	239 to 266	253
		2.11	Week 40	267 to 294	281
		2.12	Week 44	295 to 322	309
		2.13	Week 48	323 to 350	337
		2.14	Week 52	351 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	

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Parameter	Analysis Phase	Scheduled Visit Number	Time Interval	Time Interval (Day)*	Target Time Point (Day)
	FU	3.1	Follow-up	End of OL+1 to End of FU	11
ECG	SCR ^a	1.1	Screening	-30 to -2	
	OL	x	Baseline (DB) ^b	<=1 [§]	
		2.1	Baseline (OL) ^c	<=1	1
		2.4	Week 12	2 to 126	85
		2.7	Week 24	127 to 210	169
		2.10	Week 36	211 to 294	253
		2.13	Week 48	295 to 350	337
		2.14	Week 52	351 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	
Weight/BMI	SCR ^a	1.1	Screening	-30 to -2	
	OL	x	Baseline (DB) ^b	<=1 [§]	
		2.1	Baseline (OL) ^c	<=1	1
		2.4	Week 12	2 to 126	85
		2.7	Week 24	127 to 210	169
		2.10	Week 36	211 to 294	253
		2.13	Week 48	295 to 350	337
		2.14	Week 52	351 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	
	FU	3.1	Follow-up	End of OL+1 to End of FU	11
MADRS, CCI CGI-S (depression), CCI (anhedonia), CCI (depression)	OL	x	Baseline (DB) ^b	<=1 [§]	
		2.1	Baseline (OL) ^c	<=1	1
		2.2	Week 4	2 to 42	29
		2.3	Week 8	43 to 70	57
		2.4	Week 12	71 to 98	85
		2.5	Week 16	99 to 126	113
		2.6	Week 20	127 to 154	141
		2.7	Week 24	155 to 182	169
		2.8	Week 28	183 to 210	197
		2.9	Week 32	211 to 238	225
		2.10	Week 36	239 to 266	253
		2.11	Week 40	267 to 294	281
		2.12	Week 44	295 to 322	309
		2.13	Week 48	323 to 350	337
		2.14	Week 52	351 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	
	FU	3.1	Follow-up	End of OL+1 to End of FU	11
SHAPS	SCR ^a	1.1	Screening	-30 to -2	

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Parameter	Analysis Phase	Scheduled Visit Number	Time Interval	Time Interval (Day)*	Target Time Point (Day)
	OL	2.1	Baseline (OL) ^c	<=1	1
		2.2	Week 4	2 to 42	29
		2.3	Week 8	43 to 70	57
		2.4	Week 12	71 to 98	85
		2.5	Week 16	99 to 126	113
		2.6	Week 20	127 to 154	141
		2.7	Week 24	155 to 182	169
		2.8	Week 28	183 to 210	197
		2.9	Week 32	211 to 238	225
		2.10	Week 36	239 to 266	253
		2.11	Week 40	267 to 294	281
		2.12	Week 44	295 to 322	309
		2.13	Week 48	323 to 350	337
		2.14	Week 52	351 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	
	FU	3.1	Follow-up	End of OL+1 to End of FU	11
PHQ-9, CCI, CCI	OL	2.1	Baseline (OL) ^c	<=1	1
		2.4	Week 12	2 to 126	85
		2.7	Week 24	127 to 210	169
		2.10	Week 36	211 to 294	253
		2.13	Week 48	295 to 350	337
		2.14	Week 52	351 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	
	FU	3.1	Follow-up	End of OL+1 to End of FU	11
ASEX	OL	x	Baseline (DB) ^b	<=1 [§]	
		2.1	Baseline (OL) ^c	<=1	1
		2.4	Week 12	2 to 126	85
		2.7	Week 24	127 to 210	169
		2.10	Week 36	211 to 294	253
		2.13	Week 48	295 to 350	337
		2.14	Week 52	351 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	
CCI, CCI, CCI (only direct-entry participants and those transferred from MDD3001)	OL	2.1	Baseline (OL) ^c	<=1	1
		2.4	Week 12	2 to 126	85
		2.7	Week 24	127 to 210	169
		2.10	Week 36	210 to 294	253
		2.13	Week 48	295 to 350	337
		2.14	Week 52	351 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	

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Parameter	Analysis Phase	Scheduled Visit Number	Time Interval	Time Interval (Day)*	Target Time Point (Day)
CCI (only direct-entry participants and those transferred from MDD3001)	OL	2.1	Baseline (OL) ^c	<=1	1
		2.7	Week 24	2 to 266	169
		2.14	Week 52	267 to End of OL	365
		OL final visit	Endpoint (OL) ^d	2 to End of OL	
CCI (CCI)	SCR ^a	1.2	Screening	-30 to -2	
	OL	2.1	Baseline (OL) ^c	<=1	1
		2.7	Week 24	2 to 182	169
		OL final visit	Endpoint (OL) ^d	2 to End of OL	
Hematology, Chemistry, Urinalysis	SCR ^a	1.1	Screening	-30 to -2	
	OL	x	Baseline (DB) ^b	<=1 [§]	
		2.1	Baseline (OL) ^c	<=1	1
		2.4	Week 12	2 to 126	85
		2.7	Week 24	127 to 210	169
		2.10	Week 36	211 to 294	253
		2.13	Week 48	295 to 350	337
		2.14	Week 52	351 to End of OL	365
PWC-20 (only direct-entry participants and those transferred from MDD3002)	OL	OL final visit	Endpoint (OL) ^d	2 to End of OL	
	FU	3.1	Follow-up	End of OL+1 to End of FU	11

^a SCR: Screening; Screening phase is for direct-entry participants only.

^b Baseline (DB) is the last assessment taken on or prior to the first dose of study intervention including the parent study (for transferred entry participants).

^c Baseline (OL) is defined as the last assessment taken on or prior to the first dose of study intervention in the open-label study.

^d Endpoint (OL) is the last observation in the OL phase.

[§] Relative to the first day of study intervention in the original study for transferred-entry participants, and the study intervention in the OL phase for the direct-entry participants.

Relative day: (event date – analysis phase start date + 1) for an event occurring on or after the analysis phase start date; (event date – analysis phase start date) for an event prior to the analysis phase start date.

* Relative to the first day of the study phase for OL visits. For the follow-up phase, time interval is relative to the first day of the follow-up phase, and Day 11 in this phase will be considered as target day if there are multiple assessments.

5.1.3. Imputation of Efficacy

Imputation of total scores of efficacy scales will be performed as shown in Table 3 below. If the number of items with missing scores is greater than the maximum number of items presented in the table, the total score will be missing.

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Table 3: Imputation of Total Score for Efficacy Scales

Efficacy Scale	Total Number of Items	Maximum Number of Items That Can Be Missing	Formula for Total Score
MADRS	10	1	Sum of non-missing item scores * (10 / number of non-missing items)
CCI	34	6	Sum of non-missing item scores * (34 / number of non-missing items)

For the remaining efficacy assessments which require adding multiple item scores, the total score will be missing if any item score is missing.

Imputation for missing data for the responder and remitter efficacy endpoints based on MADRS total score and PHQ-9 total score is presented in [Table 4](#).

Table 4: Imputation of Missing Efficacy Data

Imputation	Method/Rule
Non-Responder	Participants with missing values will be imputed as non-responders.
Non-Remitter	Participants with missing values will be imputed as non-remitters.

5.2. Participant Dispositions

The number of screened participants and reason for screen failures will be summarized overall for direct-entry and transferred-entry participants.

The number of transferred-entry participants and direct-entry participants will be provided.

The number of participants in the following disposition categories will be summarized throughout the study by treatment sequence and overall for the safety analysis set:

- Participants who received study intervention
- Participants who completed, discontinued and reasons for discontinuation from the study intervention during the open-label treatment phase
- Participants who completed, discontinued and reasons for discontinuation of study

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who discontinued from study prematurely

If deemed necessary, additional analyses of disposition data for assessing and mitigating the impact of COVID-19 on study outcome will be conducted as presented in [section 6.9](#).

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5.3. Efficacy Endpoint(s) Analysis

The following efficacy evaluations will be summarized descriptively at each scheduled visit by treatment sequence using observed data (unless otherwise specified) for the following: Depression symptoms using the MADRS as well as a patient-reported outcome (PHQ-9), anhedonia symptoms using CCI and global change in severity (CGI-S). The proportion of participants who responded and remitted based on the MADRS total score and PHQ-9 will be provided over time.

The summaries of efficacy endpoints below will be provided for the FAS_ANH+ and FAS_All analysis sets, unless otherwise specified. Additionally, summaries of MADRS and CCI will be provided for the FAS_ANH+_e analysis set as noted below.

5.3.1. MADRS**5.3.1.1. Definition**

The 10-item clinician-administered Montgomery-Asberg Depression Rating Scale (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 will 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. All MADRS assessments may be video-recorded for the purpose of quality monitoring.

Negative changes in MADRS total score indicate improvement.

A participant is defined as a responder at a given time point if the percent improvement from baseline (DB/OL) in MADRS total score is $\geq 50\%$.

A participant is defined as a remitter at a given time point if the MADRS total score of ≤ 10 at that time point.

5.3.1.2. Analysis Methods

Descriptive statistics of the total score will be provided over time from baseline (DB) through each time point during DB phase (transfer entry participants only), OL treatment phase and follow-up

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phase, and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase for FAS_ANH+ and FAS_All analysis sets. To assess the treatment effect in participants without anhedonia, the analysis will be repeated for the MDD_WOANH_S and MDD_WOANH_MS analysis sets. In addition, the proportion of participants who responded and remitted based on the MADRS total score will be provided over time for each phase for FAS_ANH+, MDD_WOANH_S, NDD_WOANH_MS, and FAS_All analysis sets. Summaries of observed data as well as imputed data ([section 5.1.5](#)) will be presented separately.

Additionally, the above analyses will be conducted for FAS_ANH+_e.

Mean ($\pm$ SE) of MADRS total score over time (from baseline (DB) through each time point during DB and OL treatment phases) will be presented graphically for FAS_ANH+ by treatment sequence.

5.3.2. PHQ-9**5.3.2.1. Definition**

The 9-item Patient Health Questionnaire, 9-item (PHQ-9) scale scores each of the 9 symptom domains of the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5th Edition) 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.

Negative changes in PHQ-9 total score indicate improvement.

A participant is defined a responder at a given time point if the percent improvement from baseline (DB/OL) in PHQ-9 total score is $\geq 50\%$.

A participant is defined as a remitter at a given time point if the PHQ-9 total score is < 5 at that time point.

5.3.2.2. Analysis Methods

Descriptive statistics of the total score will be provided over time from baseline (DB) through each time point during DB phase (transfer entry participants only), OL treatment phase and follow-up phase, and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase.

The above analyses will be conducted for FAS_ANH+_e.

Mean ($\pm$ SE) of PHQ-9 total score over time (from baseline (DB) through each time point during DB and OL treatment phases) will be presented graphically for FAS_ANH+ by treatment sequence.

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In addition, the proportion of participants who responded and remitted based on the PHQ-9 total score will be provided over time for each phase. Summaries of observed data as well as imputed data ([section 5.1.5](#)) will be presented separately.

Additionally, the proportion of participants with a score of ≥ 2 at baseline (DB) but less than 2 in the PHQ-9 anhedonia-specific item (item 1) over time will be provided for the OL treatment phase.

5.3.3. CCI**5.3.3.1. Definition**

CCI

[Redacted text block]

5.3.3.2. Analysis Methods

Descriptive statistics of the CCI total score will be provided over time from baseline (DB) through each time point during DB phase (transfer entry participants only), OL treatment phase and follow-up phase, and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase for FAS_ANH+ and FAS_All analysis sets. To assess the treatment effect in participants without anhedonia, the analyses will be repeated for the MDD_WOANH_S and MDD_WOANH_MS analysis sets.

The above analyses will be conducted for FAS_ANH+_e.

Mean ($\pm$ SE) of CCI total score over time (from baseline (DB) through each time point during DB and OL treatment phases) will be presented graphically over time for FAS_ANH+ by treatment sequence.

Additionally, change from baseline (OL) over time in the subscales of the CCI will also be provided.

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5.3.4. CGI-S**5.3.4.1. Definition**

The Clinical Global Impression-Severity (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.

Negative changes in CGI-S score indicate improvement.

5.3.4.2. Analysis Methods

Descriptive statistics of the total score will be provided over time from baseline (DB) through each time point during DB phase (transfer entry participants only), OL treatment phase and follow-up phase, and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase.

The above analyses will be conducted for FAS_ANH+_e.

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

5.4. Exploratory Endpoint(s) Analysis

The following efficacy evaluations will be summarized descriptively at each scheduled visit by treatment sequence using observed data (unless otherwise specified) using the following: measurements of anhedonia (SHAPS), global change in two CCI items for anhedonia and depression, family functioning related disability (CCI health-related quality of life (CCI health status (CCI work functioning and productivity (CCI anxiety (CCI and treatment satisfaction (CCI

The assessment of exploratory endpoints below will be conducted on the FAS_ANH+ and FAS_All analysis sets.

5.4.1. SHAPS**5.4.1.1. Definition**

The Snaith-Hamilton Pleasure Scale (SHAPS) (Nakonezny 2010, Snaith 1995) is a self-report 14-item, instrument, developed for the assessment of hedonic capacity. The SHAPS is a validated scale for the measurement of anhedonia. It has excellent internal consistency, with construct validity, and is unidimensional in assessing hedonic capacity among adult patients with MDD. The

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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 a “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).

Remitted MDD patients had a mean SHAPS total score of 21.2 (95% CI 20.5-22.0), which was comparable to healthy controls with no anhedonia (20.2; 95% CI: 19.7-20.8). Therefore, a SHAPS total score below 22 is being used to indicate no anhedonia (Trostheim, 2020).

Negative changes in SHAPS total score indicate improvement.

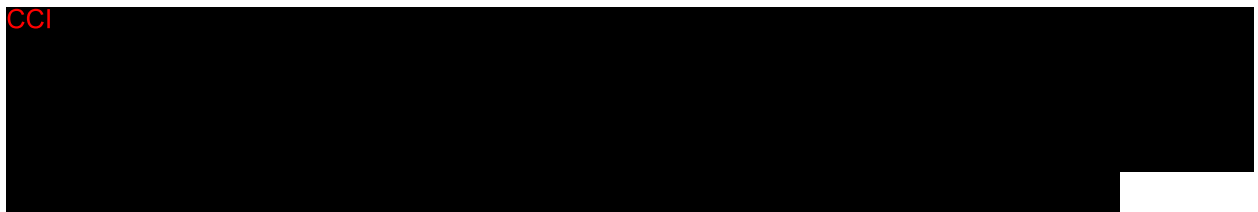
5.4.1.2. Analysis Methods

Descriptive statistics of the total score and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase. The proportion of participants with SHAPS total score below 22 over time will also be provided during OL treatment phase and follow-up phase.

Mean ($\pm$ SE) of SHAPS total score over time will be presented graphically for the FAS_ANH+ analysis set.

5.4.2. CCI**5.4.2.1. Definition**

CCI

**5.4.2.2. Analysis Methods**

Descriptive statistics of the total score and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase.

A frequency distribution of the CCI scores for anhedonia and depression over time will be provided. The frequencies of CCI scores for anhedonia and depression will be plotted at baseline (OL) and endpoint (OL) for the FAS_ANH+ analysis set.

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5.4.3.

CCI [REDACTED]

5.4.3.1.**Definition**

CCI [REDACTED]

5.4.3.2. Analysis Methods

Descriptive statistics of the CCI [REDACTED] total score and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase.

Mean ($\pm$ SE) of the T-scores over time will be presented graphically for the FAS_ANH+ analysis set.

5.4.4.

CCI [REDACTED]

5.4.4.1.**Definition**

CCI [REDACTED]

| [REDACTED]

| [REDACTED]

| [REDACTED]

| [REDACTED]

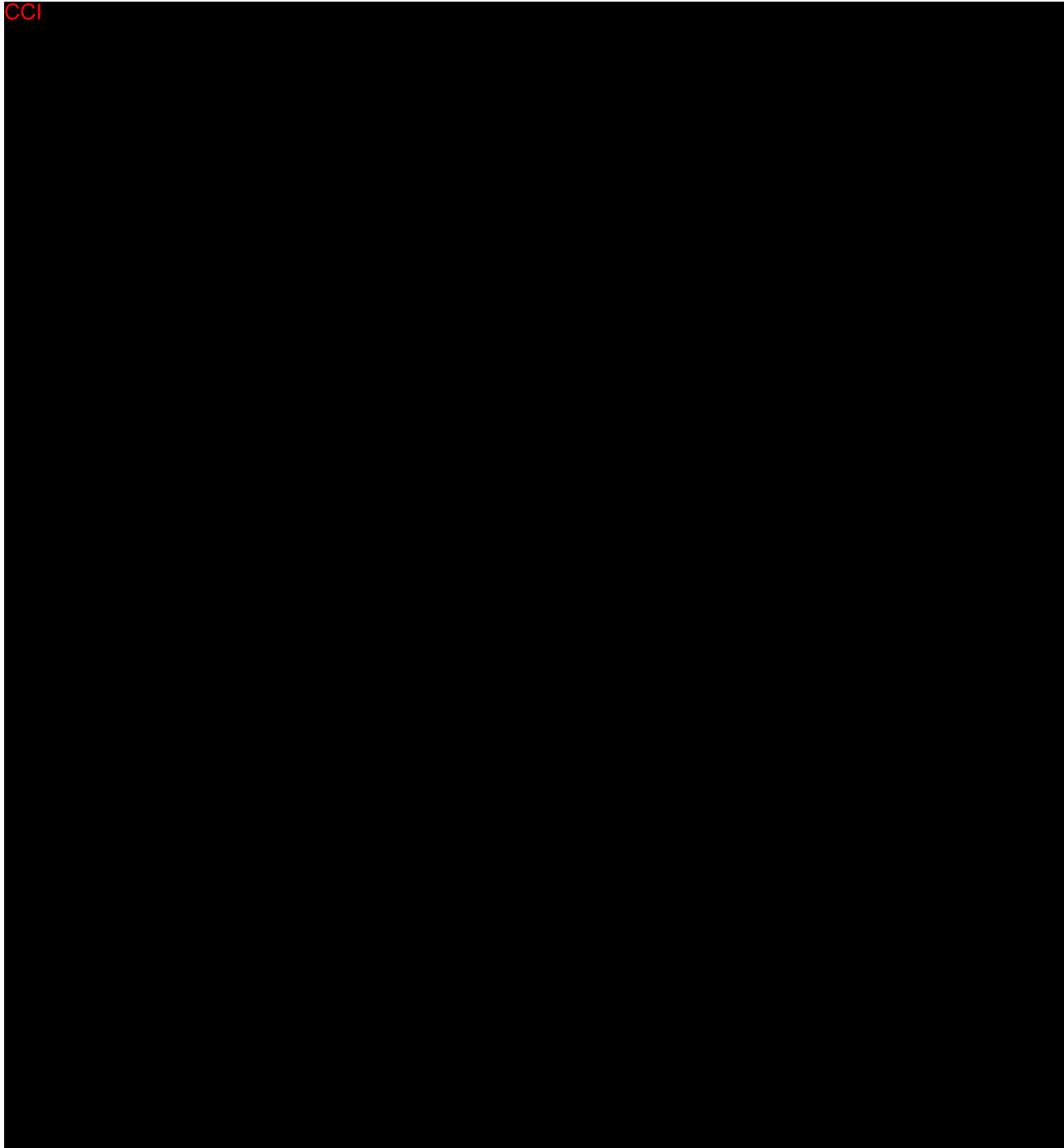
5.4.4.2. Analysis Methods

In this study, this assessment will be performed only for the direct-entry participants and those transferred from Study 67953964MDD3001.

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Descriptive statistics of the actual values and the change from baseline (OL) over time during the OL treatment phase and follow-up phase will be presented for work time missed, work impairment, overall work impairment and activity impairment by treatment sequence.

Mean ($\pm$ SE) of work impairment and activity impairment over time will be presented graphically for the FAS_ANH+ analysis set.

5.4.5. CCI **5.4.5.1. Definition**CCI 

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5.4.5.2. Analysis Methods

Descriptive statistics of the actual values and the change from baseline (OL) to each postbaseline time point in the OL treatment phase and follow-up phase will be presented by treatment sequence for weighted EQ-5D health status index, the EQ-VAS, and the sum score.

In addition, individual dimension responses using a frequency distribution will also be summarized for each visit for all phases, including the follow-up phase. The frequencies of individual responses will be plotted at baseline (OL) and endpoint (OL) for the FAS_ANH+ analysis set.

5.4.6. CCI**5.4.6.1. Definition**

CCI

5.4.6.2. Analysis Methods

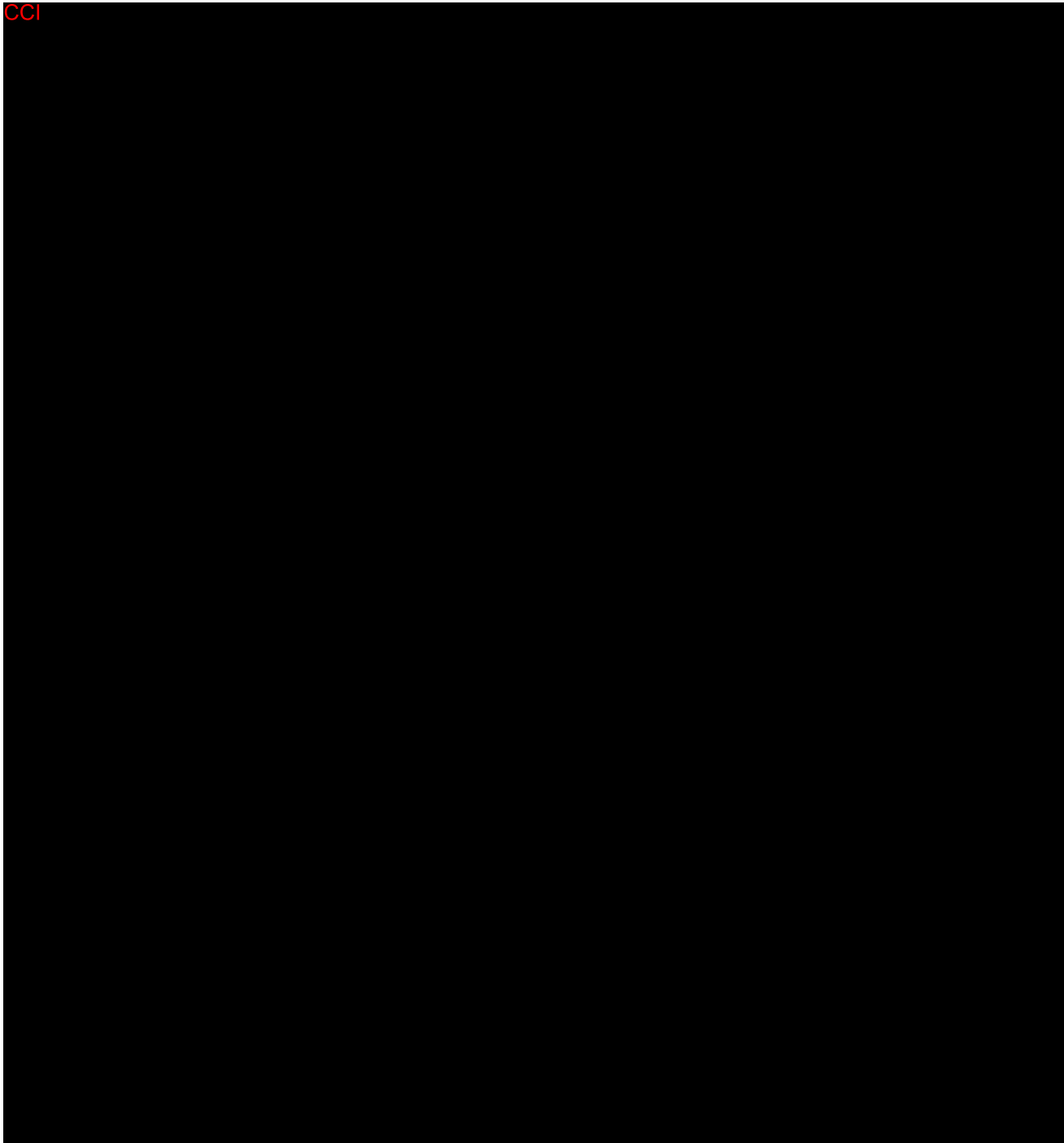
Descriptive statistics of the total score and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase.

5.4.7. CCI**5.4.7.1. Definition**

CCI

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CCI



5.4.7.2. Analysis Methods

In this study, this assessment will be performed only for the direct-entry participants and those transferred from 67953964MDD3001.

Descriptive statistics of scores at Week 24 and End-of-Treatment will be provided.

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5.4.8. CCI**5.4.8.1. Definition**

CCI

5.4.8.2. Analysis Methods

Descriptive statistics of the total score and change from baseline (OL) over time will be provided for each visit during OL treatment phase and follow-up phase.

5.5. Safety Analyses

All safety analyses will be based on the safety analysis set or follow-up analysis set, unless otherwise specified.

Safety summaries will be provided for the OL treatment phase and follow-up phase. For safety summaries, the data will be presented by treatment sequence based on the randomized treatment group in the parent study as indicated in the relevant sections below.

For all continuous safety variables, descriptive statistics by treatment sequence will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by treatment sequence using frequency counts and percentages.

5.5.1. Extent of Exposure

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

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

Duration of intervention will be summarized in the following duration categories: [0-4 weeks, >4-8 weeks, >8-12 weeks, >12-16 weeks, >16-20 weeks, >20-24 weeks, >24-28 weeks, >28-32 weeks, >32-36 weeks, >36-40 weeks, >40-44 weeks, >44-48 weeks, >48-52 weeks, >52 weeks].

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) +1. Total dosing days of intervention is defined as the total number of days that study intervention was administered to the participant (excluding days off study intervention).

Current antidepressant duration is defined as (minimum of end of open-label phase and end of antidepressant use – maximum of start of open-label phase and start of antidepressant use) +1.

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A frequency distribution of participants with 6 months (26 weeks) and 12 months (52 weeks) of study intervention exposure will be provided.

5.5.2. Compliance

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

The percent compliance will be categorized (<60%, 60-<80%, 80-<100%, >=100%) and the number and percentage of participants in each category will be summarized for study intervention and for the current antidepressant.

Compliance will be calculated for the study intervention as:

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

Compliance will be calculated for the current antidepressant regardless of the switch of antidepressant as shown below. On days where more than one antidepressant is taken, each day of overlap will be counted once:

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

5.5.3. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention through the end of OL treatment phase is considered to be treatment emergent. If the AE occurs on the day of the initial administration of study intervention (and the action taken entered in the database is not 'Not Applicable'), then the event will be assumed to be treatment emergent. If the AE date is recorded as partial or completely missing, then the AE will be considered to be treatment-emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported adverse events will be included in the analysis. For each adverse event and AESI, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by treatment sequence.

For transferred-entry subjects, the number (%) of adverse events ongoing at the time of entry into the MDD3003 study will be summarized separately.

Assignment of adverse events to the appropriate phase will be made based on the following rules:

Open-label analysis phase:

- For participants who are ongoing in the OL treatment phase at the data cut-off date for the interim lock (see [section 5.7](#)): OL phase start date ≤ AE onset date ≤ data cut-off date

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- For participants who completed/discontinued from the OL treatment phase: OL phase start date $\leq$ AE onset date $\leq$ OL phase end date

Follow-up phase:

- AEs that are assigned to the follow-up phase are not considered as treatment-emergent. AEs with onset date $\geq$ follow-up phase start date will be assigned to this phase.

Summary tables will be provided for treatment-emergent adverse events:

- AEs (all AEs, and AEs with incidence of at least 5% in any treatment group)
- Serious AEs (SAEs)
- AEs leading to discontinuation of study intervention
- AEs by severity
- AEs by relationship to study intervention
- AEs leading to treatment interruption
- Severe AEs
- CCl AEs that were treated with a medication
- AEs of special interest (AESI)
 - Special interest of AE includes CCl [REDACTED] and CCl [REDACTED]
- AEs of clinical interest
 - CCl organ class AEs
 - Suicide/Self-injury (First Sub SMQ)
 - AEs suggestive of abuse potential (identified in [section 6.7](#))

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

- Died
- Had SAEs
- Had AEs leading to discontinuation of study intervention
- Had AEs of special interest
 - Special interest of AE includes CCl [REDACTED] and CCl [REDACTED]
- Had AEs of clinical interest
 - CCl organ class AEs
 - Suicide/Self-injury (First Sub SMQ)
 - AEs suggestive of abuse potential (identified in [section 6.7](#))

AEs and AESIs will also be summarized separately based on safety analysis set (elderly).

In addition, for each AESI, the number of days of dosing prior to onset, duration of the event, frequency distribution of the number of occurrences, and number of participants who were treated with concomitant medications will be summarized. Number, distribution, and intensity of CCl episodes with an onset after the first dose of aticaprant will be summarized. For CCl organ class AEs, number of participants who were treated with concomitant medications will also be summarized.

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5.5.4. Additional Safety Assessments**5.5.4.1. Clinical Laboratory Tests**

Descriptive statistics for all chemistry, hematology, and urinalysis laboratory tests, and change from baseline (OL) will be presented at scheduled time points in the OL treatment phase by treatment sequence.

Clinical laboratory test values will be considered “treatment-emergent markedly abnormal” (TEMA) using the criteria defined by the sponsor listed in [section 6.8](#).

- If the postbaseline value is above the upper limit of the markedly abnormal criteria and the baseline (DB/OL) value is below the upper limit, then the postbaseline marked abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit of the markedly abnormal criteria with the baseline (DB/OL) value being above the lower limit of the markedly abnormal criteria.
- If the baseline (DB/OL) value is missing, a postbaseline marked abnormality will always be considered as TE.

The number and percentage of participants with treatment-emergent markedly abnormal values will be presented. This analysis will be conducted for all participants and separately for the participants who experience  AEs.

For the value to be flagged as ‘markedly abnormal’ the baseline (DB/OL) value should be $\leq$ the critical values or the baseline (DB/OL) value can be missing, and the post-baseline values should be greater than the critical values.

Incidence of participants with ALT values $\geq 3 \times$ upper normal limit (ULN), AST values $\geq 3 \times$ ULN, total bilirubin values $\geq 2 \times$ ULN (or at least doubling of direct bilirubin in known Gilbert’s syndrome), and international normalized ratio (INR) > 1.5 (if measured) will be presented for OL treatment phase. Additionally, incidence of hepatic toxicity (Hy’s Law) defined as ALT or AST values $\geq 3 \times$ ULN AND alkaline phosphatase $< 2 \times$ ULN AND (total bilirubin values $\geq 2 \times$ ULN OR INR > 1.5 , if measured) will be presented. Participants with baseline (DB/OL) values meeting these criteria will not be considered as having treatment-emergent hepatic toxicity.

A listing of participants with markedly abnormal laboratory values will be provided. A listing of participants with ALT $\geq 3 \times$ ULN or AST values $\geq 3 \times$ ULN) and participants with hepatic toxicity (suspected Hy’s Law cases) will be provided.

The incidence of treatment-emergent markedly abnormal laboratory values at any time during the open-label phase will also be presented for the safety analysis set (elderly).

5.5.4.2. Vital Signs and Physical Examination Findings

Descriptive statistics (mean, standard deviation, median, minimum and maximum) of body weight, temperature, pulse/heart rate, respiratory rate, pulse oximetry and blood pressure (systolic and

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diastolic) values, and change from baseline (OL) will be presented for the scheduled time points in the open-label and follow-up phases by treatment sequence. Changes from baseline (OL) in body weight and BMI will be summarized descriptively.

Any treatment-emergent abnormality will be listed.

The proportion of participants with treatment-emergent abnormal vital signs will be summarized for the open-label phase. Post-baseline values in each phase will be compared with the baseline (DB/OL) values based on the criteria described in Table 5. The abnormality will be considered as treatment-emergent if the postbaseline value is above the upper limit and the baseline (DB/OL) value is below the upper limit (eg, Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline (DB/OL) value being above the lower limit (eg, Normal or High). If the baseline (DB/OL) value is missing, a postbaseline abnormality will always be considered as treatment-emergent.

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

Table 5: Clinically Important/Markedly Abnormal Vital Signs

Vital Sign	Abnormal Category	Criteria
Pulse	Abnormally high	≥ 100 bpm and with ≥ 15 bpm increase from baseline
	Abnormally low	≤ 50 bpm and with ≥ 15 bpm decrease from baseline
Systolic blood pressure	Abnormally high	≥ 180 mm Hg and with ≥ 20 mm Hg increase from baseline
	Abnormally low	≤ 90 mm Hg and with ≥ 20 mm Hg decrease from baseline
Diastolic blood pressure	Abnormally high	≥ 105 mm Hg and with ≥ 15 mm Hg increase from baseline
	Abnormally low	≤ 50 mm Hg and with ≥ 15 mm Hg decrease from baseline
Temperature	Abnormally high	$> 37.5^{\circ}\text{C}$
	Abnormally low	$< 35.5^{\circ}\text{C}$
Weight	Abnormally high	increase 7% from baseline
	Abnormally low	decrease 7% from baseline

The incidence of treatment-emergent markedly abnormal vital signs at any time during the open-label phase will also be presented separately for the safety analysis set (elderly).

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5.5.4.3. Electrocardiogram

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:

Bazett's formula: $QTcB \text{ (msec)} = QT \text{ (msec)} / (RR \text{ (msec)}/1000)^{1/2}$; if RR is missing, use $QT \text{ (msec)} * (HR(bpm)/60)^{1/2}$;

Fridericia's formula: $QTcF \text{ (msec)} = QT \text{ (msec)} / (RR \text{ (msec)}/1000)^{1/3}$; if RR is missing, use $QT \text{ (msec)} * (HR(bpm)/60)^{1/3}$.

Baseline for the direct-entry participants is the most recent assessment prior to the first dose, or average of the most recent assessments prior to the first dose if multiple assessments are done on the same day. The baseline from the parent studies will be used as the baseline for transferred-entry participants. Postbaseline abnormalities will be compared with their corresponding baseline result. Abnormal ranges for the HR, PR, QRS and QT intervals are given in [Table 6](#).

Descriptive statistics of QTc intervals, and changes from baseline will be summarized at each scheduled time point by treatment sequence.

Criteria for abnormal corrected QT intervals and changes from baseline are given in [Table 6](#) (the same criteria apply to all QT corrections).

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.

Table 6: Criteria for Abnormal QTc Values and Changes from Baseline

Parameter	Classification	Criteria
QTc change from baseline	No Concern	≤ 30
	Concern	$> 30 - 60$
	Clear Concern	> 60
QTc value	Normal	≤ 450 for male, ≤ 470 for female
	$> 450 - 480$ for male, $470 - 480$ for female	> 450 to ≤ 480 for male, > 470 to ≤ 480 for female
	$> 480 - 500$	$> 480 - \leq 500$
	> 500	> 500

Descriptive statistics of ECG parameters and change from baseline will be summarized at each scheduled time point for OL treatment phase. Shift from baseline to maximum postbaseline QTc interval will be summarized during OL treatment phase.

The frequency of treatment-emergent abnormalities will be tabulated and presented. The identification of treatment-emergent abnormal ECG values is based on the post-baseline value (a

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value occurring after the start of the phase) being out of range while the baseline value is either missing or within the limits given in Table 7. If post-baseline ECG results are above the upper limits (abnormally high) and the baseline value is below the lower limits (abnormally low), then the post-baseline abnormality will also be considered treatment-emergent. The same applies to the post-baseline value being below the lower limits (abnormally low) with the baseline value being above the upper limits (abnormally high).

Table 7: Abnormal Limits for ECG Parameters

ECG Parameter	Abnormally Low	Abnormally High
HR (bpm)	≤ 50 bpm	≥ 100 bpm
PR interval (msec)	≤ 120 msec	≥ 200 msec
QRS interval (msec)	≤ 60 msec	≥ 120 msec
QT interval (msec)	≤ 200 msec	≥ 500 msec
RR interval (msec)	≤ 600 msec	≥ 1200 msec

The interpretation of the ECGs as determined by a central reader will be displayed by the number and percentage of participants meeting the normality criteria. The interpretation will be summarized over time.

A listing of clinically relevant ECG abnormalities (see Table 7) will also be provided.

The incidence of treatment-emergent abnormalities will also be presented separately for the safety analysis set (elderly).

5.5.4.4. Other Safety Parameters**5.5.4.4.1. Columbia Suicide Severity Rating Scale (C-SSRS)**

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 intervention (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.

Suicidal Ideation (1-5)	
1	Wish to be dead
2	Non-specific active suicidal thoughts
3	Active suicidal ideation with any methods (not plan) without intent to act
4	Active suicidal ideation with some intent to act, without specific plan
5	Active suicidal ideation with specific plan and intent
Suicidal Behavior (6-10)	
6	Preparatory acts or behavior
7	Aborted attempt
8	Interrupted attempt

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9	Actual attempt
10	Suicide
Non-suicidal self-injurious behavior (11)	
11	Non-suicidal self-injurious behavior

At each time point, an event of suicidal ideation or behavior will be assigned a score of 1 to 10 based on the maximum response for the C-SSRS at that visit. If there is no event of suicidal ideation or behavior, a score of 0 will be assigned (0=“no suicidal ideation or behavior that can be assessed on the basis of C-SSRS”). A participant with an event of non-suicidal self-injurious behavior only will not be considered as having suicidal ideation or behavior, therefore a score of 0 will be assigned. However, an additional score of 11 will be assigned to summarize any participants with an event of non-suicidal self-injurious behavior. Shifts from the baseline (DB/OL) to the maximum postbaseline score pertaining to suicidal ideation or suicidal behavior (i.e., scores 1 to 10) will be summarized for each phase.

The maximum score (of scores 0 to 10) assigned to each participant will be grouped into one of three broad categories: No suicidal ideation or behavior (0), Suicidal ideation (1-5), Suicidal behavior (6-10). Shifts from baseline (DB/OL) to the maximum postbaseline category will be summarized for each phase.

A frequency distribution of the scores for the 11 categories (0 to 10) will be provided by study intervention at each time point for each phase. In addition, the number and proportion of participants with non-suicidal self-injurious behavior (a score of 11) will be provided at each time point for each phase.

Shifts from baseline (DB/OL) to suicidal ideation or suicidal behavior (as described above) will also be summarized for safety analysis set (elderly).

A listing of potentially suicidal ideation, suicidal behavior, or non-suicidal self-Injurious behavior will be provided for subjects who had at least one event during the study.

5.5.4.4.2. 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. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. The scale has shown satisfactory reliability and validity ([McGahuey 2000](#)). The ASEX has a recall period of the past week.

Each of the 5 items is rated on a 6-point Likert scale, ranging from 1 to 6. The total score is the sum of the 5 items. Possible total scores range from 5 to 30, with the higher scores indicating more sexual dysfunction. If any item of the scale is missing at a visit, the total score for that scale at that visit will be left blank.

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For each of the 5 items, a frequency distribution will be provided by gender at each time point during open-label phase. In addition, for each of the 5 items, a frequency distribution will be provided, combining the responses for the genders. For this analysis, “vaginal lubrication/penile erection” (question 3) will be summarized as one question.

The number and percentage of participants who have ASEX total score 19 or greater, or a score of 5 or greater on any item, or a score of 4 or greater on any 3 items, reflecting sexual dysfunction, will be summarized at each time point by treatment sequence for the OL treatment phase. This analysis will be repeated for the following subgroups:

- Responder status based on MADRS total score at the end of the parent study (responder, non-responder)
- Sex (male, female)
- Age (18-44 years, 45-64 years, 65-74 years)

5.5.4.4.3. 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 Time and Events Schedule only for female participants with a menstrual cycle.

Descriptive summary statistics (n, mean, SD, median, minimum, and maximum) of the length of menstrual cycle will be summarized by exposure category (ex: 1-day – 4 weeks, >4 weeks – 8 weeks, and so on) and treatment sequence. The exposure categories will be determined in relation to the date of first dose of aticaprant, which is the date of first exposure in the parent study for participants randomized to aticaprant in the parent study, and date of first exposure in the current study for participants randomized to placebo in the parent study and direct entry participants (if any). Only the menses which had an onset while on study medication (in the parent or the current study) will be included in the analysis. The average length of menstrual cycle collected at screening will be used as the baseline. For participants who experienced more than one menses within an exposure category, the length will be averaged across the menstrual cycles.

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

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](#)).

In this study, this assessment will be performed only for the direct-entry participants and those transferred from Study 67953964MDD3002. The frequency of withdrawal symptom after discontinuation from the OL treatment phase and FU phase will be summarized by treatment sequence.

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In addition, symptoms at follow-up will be compared to endpoint (OL) for the follow-up analysis set and will be summarized using the following categories: new or worsened symptoms, symptoms present and unchanged, no symptoms, and improved.

5.6. Other Analyses**5.6.1. Biomarkers****▪ 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.

Mean ($\pm$ SE) of MADRS total score over time (from baseline (DB) time point during DB phase) will be presented graphically for individuals positive for the biosignatures (MDD Sig+) by treatment sequence. Mean ($\pm$ SE) of MADRS total score over time (from baseline (DB) time point during DB phase) will also be presented graphically for individuals negative for the biosignatures (MDD Sig-) by treatment sequence.

5.6.2. Exploratory Biomarker Analyses

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

5.6.3. 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.

5.6.4. Subgroups Analyses

Subgroup summaries of the efficacy endpoints (MADRS and CCI) will be provided for the FAS_ANH+ analysis set for the following subgroups:

- Sex (male, female, unknown, undifferentiated)
- Race (Black or African American, White, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- Country/territory
- Region (South America, North America, Europe, Asia, Other)
- Age Group (18-44 years, 45-64 years)
- BMI (underweight <18.5 kg/m², normal 18.5-<25 kg/m², overweight 25-<30 kg/m², obese 30-<40 kg/m², morbidly obese $\geq$ 40 kg/m²)
- Number of major depressive episodes (1, 2-5, 6-10, >10)

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- Current antidepressant type (SSRI, SNRI)

5.7. Interim Analyses

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 in order to support filing in the ROW. If necessary, other interim lock(s) may be implemented once all the participants in Japan and/or China have completed at least 6 months of study participation depending on the requirement by the respective health authorities.

5.7.1. Data Monitoring Committee (DMC) or Other Review Board

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

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6. SUPPORTING DOCUMENTATION**6.1. Appendix 1 List of Abbreviations**

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANH+	with moderate-to-severe anhedonia
ASEX	Arizona Sexual Experiences Scale
AST	aspartate aminotransferase
ATC	anatomic and therapeutic class
AUC	area under the curve
BMI	body mass index
CGI-S	Clinical Global Impression - Severity
CRF	case report form
CSR	Clinical Study Report
C-SSRS	Columbia Suicidality Severity Rating Scale
CCI	CCI
DB	double-blind
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
DSM-5	Diagnostic and Statistical Manual of Mental Disorders-5th Edition
ECG	electrocardiogram
eCRF	electronic case report form
CCI	EuroQol-5 Dimension-5 Level
EW	early withdrawal
FAS	full analysis set
FDA	Food and Drug Administration
CCI	CCI
HDRS-17	17-item Hamilton Depression Rating Scale
iARBM	Integrated Analytical Risk-Based Monitoring
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
MADRS	Montgomery-Åsberg Depression Rating Scale
MDD ANH+	MDD with moderate-to-severe anhedonia (ANH+)
MDD ANH-	MDD without moderate-to-severe anhedonia (ANH-)
MDD_WOANH_MS	MDD without anhedonia (based on SHAPS/SCID-T while thresholding by MADRS)
MDD_WOANH_S	MDD without anhedonia (based on SHAPS)
MDD3001	67953964MDD3001 (study number)
MDD3002	67953964MDD3002 (study number)
MDD3003	67953964MDD3003 (study number)
MedDRA	Medical Dictionary for Regulatory Activities
MGH ATRQ	Massachusetts General Hospital Antidepressant Treatment Response Questionnaire
non-PAP	Non primary analysis population
NSAIDs	Non-steroidal anti-inflammatory drugs
OL	open-label
PD	pharmacodynamic(s)
CCI	CCI
PHQ-9	Patient Health Questionnaire, 9-item
PRO	Patient-Reported Outcome(s) (paper or electronic as appropriate for this study)
PROMIS	Patient-Reported Outcomes Measurement Information System
CCI	CCI
CCI	CCI
PWC-20	Physician Withdrawal Checklist, 20-item
CCI	CCI
QTL	Quality Tolerance Limit

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ROW	rest of the world
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID-CT	Structured Clinical Interview for DSM-5 Axis I Disorders-Clinical Trials version
SD	standard deviation
SHAPS	Snaith-Hamilton Pleasure Scale
SIQA	Site Independent Qualification Assessment
SMQs	standardized MedDRA queries
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TEAE	treatment-emergent adverse event
CCI	CCI
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary
CCI	CCI

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6.2. Appendix 2 Changes to Protocol-Planned Analyses

The analysis of exploratory endpoints on the MDD ANH- population (now referred to as non-PAP) stated in the protocol will not be performed as this population contains participants with prominent anhedonia (i.e., SHAPS $\geq$ 32). However, these participants will be included in the All MDD population.

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6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized. In addition, the distribution of participants by region, country/territory, and site ID will be presented.

Table 8 presents a list of the demographic variables that will be summarized for the FAS_ANH+, MDD_WOANH_S, MDD_WOANH_MS, FAS_ANH+_e, and safety analysis sets.

Table 8: Demographic Variables

Continuous Variables:	Summary Type
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (kg/m ²)	
Categorical Variables	
Age group: 18-44, 45-64, 65-74	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female, unknown, undifferentiated)	
Race ^a (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple, Not Reported)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)	
BMI (underweight <18.5 kg/m ² , normal 18.5-<25 kg/m ² , overweight 25-<30 kg/m ² , obese 30-<40 kg/m ² , morbidly obese ≥40 kg/m ²)	
Country/territory	
Region (South America, North America, Europe, Asia, Other)	
Employment status (any type of employment, any type of unemployment, other) ^b	

^a If multiple race categories are indicated, the Race is recorded as 'Multiple'.

^b Any type of employment includes: any category containing “Employed”, Sheltered Work, Housewife or Dependent Husband, and Student; any type of unemployment includes: any category containing “Unemployed”; Other includes: Retired and No Information Available.

Table 9a presents a list of the disease characteristic variables that will be summarized only at baseline (OL) for the FAS_ANH+, MDD_WOANH_S, MDD_WOANH_MS, FAS_ANH+_e and safety analysis sets. Additionally, Table 9b presents a list of disease characteristic variables will be summarized both at baseline (DB) and baseline (OL) for the FAS_ANH+, MDD_WOANH_S, MDD_WOANH_MS, FAS_ANH+_e and safety analysis sets.

VENTURA-LT**Table 9a: Psychiatric History at Baseline (OL)**

Continuous Variables	Summary Type
Age (years) when diagnosed with MDD	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Duration (weeks) of current depressive episode	
Baseline SHAPS total score	
Baseline CCI score: anhedonia	
Baseline CCI score: depression	
Categorical Variables	Frequency distribution with the number and percentage of participants in each category.
Number of major depressive episodes (1, 2-5, 6-10, >10)	
Current antidepressant type (SSRI/SNRI)	
Number of prior antidepressants (0, 1, 2, 3, >3)	
Number of classes of previous ADs received prior to the current AD	
Frequency of participants who were on psychotherapy at the start at treatment	
Baseline CGI-S score (Normal (not at all ill), Borderline mentally ill, Mildly ill, Moderately ill, Markedly ill, Severely ill, Among the most extremely ill patients)	
Screening C-SSRS category (no event, suicidal ideation, suicidal behavior)	
SCID-CT DSM-5 MDD specifiers for MDD	
Overall Severity of Anhedonia (Mild, Moderate, Severe, Very severe)*	
Baseline CCI score: anhedonia (None, Mild, Moderate, Severe, Very severe)	
Baseline CCI score: depression (None, Mild, Moderate, Severe, Very severe)	
Family history of	
Alcohol Abuse (Yes, No)	
Anxiety Disorder (Yes, No)	
Bipolar Disorder (Yes, No)	
Depression (Yes, No)	
Schizophrenia (Yes, No)	
Substance Abuse (Yes, No)	
Tabacco usage (Yes, No)	

* Overall Severity of Anhedonia is based on the most impacted features of interest, motivation, engagement/effort and enjoyment/pleasure.

Table 9b: Psychiatric History at Baseline (DB) and Baseline (OL)

Continuous Variables	Summary Type
Baseline MADRS total score	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]).
Baseline CCI total score	
Baseline CGI-S score	
Baseline PHQ-9 total score	

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6.4. Appendix 4 Protocol Deviations and Quality Tolerance Limits (QTL)

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

Number of participants not meeting inclusion criteria, or meeting exclusion criteria will be summarized for the safety analysis set.

If deemed necessary, additional analyses of protocol deviations for assessing and mitigating the impact of COVID-19 on study outcome will be conducted as presented in [section 6.9](#).

Quality Tolerance Limit parameters and thresholds are defined and will be monitored in this study. QTL parameters will be summarized. More details are described in the Integrated Analytical Risk-Based Monitoring (iARBM) Plan.

6.5. Appendix 5 Prior and Concomitant Medications

Prior medications and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications will be summarized for the direct entry participants. Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by ATC level 2 and level 4 terms and base preferred term for the double-blind and follow-up phases for safety and follow-up analysis sets, respectively. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. In addition, concomitant medications of special interest will be summarized. See [section 6.6 Medications of Special Interest](#) for list of categories of medications of special interest.

Prior antidepressant medications, prior medications other than antidepressants, and prior medications of special interest will be summarized by ATC level 2 and level 4 terms and base preferred term.

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6.6. Appendix 6 Medications of Special Interest

Categories for medications of special interest are defined as follows:

Medications of Special Interest Category	
Antidepressants	
Hypnotic/sedative including z-drugs	
CCI	
CCI	
Medications for treatment of CCI	
Medications for treatment of CCI	

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6.7. Appendix 7 AE Suggested to Abuse Potential (PTs)

Potential abuse-related AEs are defined as below:

- SMQ - “Drug Abuse, Dependence and Withdrawal”
- SMQ - “Psychosis and Psychotic Disorders”
- MedDRA preferred terms (PTs):
 Aggression; Confusional state; Decreased activity; Dependence; Disorientation; Dissociation; Dissociative disorder; Dizziness; Drug abuse; Drug abuser; Drug dependence; Drug detoxification; Drug diversion; Drug rehabilitation; Drug tolerance; Drug tolerance increased; Drug use disorder; Drug withdrawal convulsions; Drug withdrawal headache; Drug withdrawal syndrome; Euphoric mood; Feeling abnormal; Feeling drunk; Feeling of relaxation; Hallucination; Hallucination, auditory; Hallucination, gustatory; Hallucination, olfactory; Hallucination, synaesthetic; Hallucination, tactile; Hallucination, visual; Hallucinations, mixed; Inappropriate affect; Mental impairment; Product tampering; Psychomotor hyperactivity; Psychotic disorder; Rebound effect; Somatic hallucination; Somnolence; Substance abuser; Substance dependence; Substance use; Substance use disorder; Substance-induced mood disorder; Substance-induced psychotic disorder; Thinking abnormal; Withdrawal arrhythmia; Withdrawal syndrome
- Standardized MedDRA Query (SMQ) and Custom MedDRA Query (CMQ) analyses:
 Dopamine dysregulation syndrome; Drug abuse; Drug abuser; Drug dependence; Drug dependence, antepartum; Drug dependence, postpartum; Drug use disorder; Drug use disorder, antepartum; Drug use disorder, postpartum; Intentional overdose; Intentional product misuse; Maternal use of illicit drugs; Neonatal complications of substance abuse; Substance abuse; Substance abuser; Substance dependence; Substance use disorder; Accidental overdose; Dependence; Disturbance in social behaviour; Drug detoxification; Drug diversion; Drug level above therapeutic; Drug level increased; Drug screen; Drug screen positive; Drug tolerance; Drug tolerance decreased; Drug tolerance increased; Intentional product use issue; Medication overuse headache; Narcotic bowel syndrome; Needle track marks; Overdose; Prescription drug used without a prescription; Prescription form tampering; Reversal of opiate activity; Substance use; Substance-induced mood disorder; Substance-induced psychotic disorder; Toxicity to various agents; Drug withdrawal convulsions; Drug withdrawal headache; Drug withdrawal maintenance therapy; Drug withdrawal syndrome; Drug withdrawal syndrome neonatal; Drug rehabilitation; Rebound effect; Steroid withdrawal syndrome; Withdrawal arrhythmia; Withdrawal catatonia; Withdrawal syndrome; Behavioural addiction; Intentional device use issue; Anti-androgen withdrawal syndrome; Intentional device misuse; Product administered at inappropriate site; Alcohol use disorder; Performance enhancing product use; Intentional misuse of drug delivery system; Cholinergic rebound syndrome; Steroid dependence; Cannabinoid hyperemesis syndrome; Delusion of parasitosis; Behavioral addiction

Note: Some of the PTs listed above are included in the *Drug Abuse, Dependence and Withdrawal*, and *Psychosis and Psychotic Disorders* SMQs

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6.8. Appendix 8 Criteria for Treatment-emergent Markedly Abnormal Laboratory Values

Laboratory Parameter	Unit	Low	High
Clinical Chemistry			
Albumin	g/dL	2.4	6.0
Albumin	g/L	24	60
Alkaline phosphatase	U/L	N/A	250
Alanine transaminase (SGPT)	U/L	N/A	200
Aspartate transaminase (SGOT)	U/L	N/A	250
Bicarbonate	mEq/L	15.1	34.9
Bicarbonate	mmol/L	15.1	34.9
Bilirubin (direct)	mg/dL	N/A	3.0
Bilirubin (direct)	μmol/L	N/A	51.3
Bilirubin (total)	mg/dL	N/A	3.0
Bilirubin (total)	μmol/L	N/A	51.3
Blood urea nitrogen	mg/dL	N/A	50
Blood urea nitrogen	mmol/L	N/A	17.9
Calcium	mg/dL	6	12
Calcium	mmol/L	1.497	2.994
Chloride	mEq/L or mmol/L	94	112
Cholesterol	mg/dL	N/A	300
Cholesterol	mmol/L	N/A	7.758
Creatine kinase	U/L	N/A	990
Creatinine	mg/dL	N/A	3
Creatinine	μmol/L	N/A	265.2
Gamma glutamyl transferase	U/L	N/A	300
Glucose Plasma	mg/dL	40	300
Glucose Plasma	mmol/L	2.204	16.653
Hemoglobin A1c	fraction of 1	0.04	0.08
High-density lipoprotein cholesterol (HDL)	mg/dL	35	N/A
High-density lipoprotein cholesterol (HDL)	mmol/L	0.905	N/A
Low-density lipoprotein cholesterol (LDL)	mg/dL	89	160
Low-density lipoprotein cholesterol (LDL)	mmol/L	2.3015	4.1376
Phosphate	mg/dL	2.2	8.1
Phosphate	mmol/L	0.71038	2.61549
Potassium	mmol/L	3.0	5.8
Sodium	mEq/L	125	155
Sodium	mmol/L	125	155
Total protein	g/L	50	N/A
Triglycerides	mg/dL	N/A	500
Triglycerides	mmol/L	N/A	5.645
Uric acid	mg/dL	1.5	10
Uric acid	μmol/L	89.22	594.8
Hematology			
Hematocrit - female	%	0.28	0.50

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- male	%	0.24	0.55
Hemoglobin	g/dL	8	19
Hemoglobin	g/L	80	190
Neutrophils	%	30	90
Monocytes	%	N/A	20
Eosinophils	%	N/A	10
Basophils	%	N/A	6
Lymphocytes	%	10	60
Reticulocytes	%	0.5	1.5
Platelet count	10 ⁹ /L; giga/L	100	600
Red blood cell (RBC) count - female	10 ¹² /L; tera/L	3.0	5.5
- male	10 ¹² /L; tera/L	3.0	6.4
White blood cell (WBC) count	10 ⁹ /L; giga/L	2.5	15.0
Urinalysis			
Urine pH		N/A	6.5
Urine specific gravity		< 1.001	> 1.035

Note: Values should be flagged as markedly abnormally low if the value is less than the value indicated in the “Low” column. Likewise, values should be flagged as markedly abnormally high if the value is greater than the value indicated in the “High” column.

Note: The same limits apply to both males and females unless gender is indicated.

N/A = Not applicable

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

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

1. Listing and summary of treatment discontinuation and study discontinuation including reasons due to COVID-19 will be presented.
2. Protocol deviation related to COVID-19 including missing visits and remote visits due to COVID will be summarized; corresponding listing will be provided.
3. Additional analyses to assess the potential impact of COVID-19 in the safety and efficacy endpoints: Mean summaries over time by types of collection (remote, home, site, etc).

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

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6.10. Appendix 10 Conversion of Raw Score to T-Score for PROMIS-APS

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

Adult version

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6.11. Appendix 11 Scoring of CCI items

I just want time to pass	True	1
	Not true	0
I feel hopeful about the future	True	0
	Not true	1
I find it hard to hold a conversation	True	1
	Not true	0
I like to know what is going on in the world	True	0
	Not true	1
I feel as if my life is wasting away	True	1
	Not true	0
I feel as if I am not in control of my life	True	1
	Not true	0
I am reluctant to leave the house	True	1
	Not true	0
On the whole, I enjoy the things I do	True	0
	Not true	1
I have lost all pleasure in life	True	1
	Not true	0
I feel as if I have nothing to offer anyone	True	1
	Not true	0
I turn away from people I care about	True	1
	Not true	0
I take good care of myself	True	0
	Not true	1
I am able to think about the future	True	0
	Not true	1
I just want to hide away	True	1
	Not true	0
I look forward to things	True	0
	Not true	1
I've forgotten what it's like to enjoy myself	True	1
	Not true	0
I can't be bothered with my friends	True	1
	Not true	0
I can cope easily with everyday tasks	True	0
	Not true	1

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I cut myself off from other people	True	1
	Not true	0
It is difficult for me to make even simple decisions	True	1
	Not true	0
I feel as if I am a burden to people	True	1
	Not true	0
Most of the time I just sit and stare into space	True	1
	Not true	0
I can't face anyone	True	1
	Not true	0
I shut everything out	True	1
	Not true	0
I'm neglecting my appearance	True	1
	Not true	0
I can see the funny side of things	True	0
	Not true	1
I don't take in what people say to me	True	1
	Not true	0
I feel as if I'm letting everyone down	True	1
	Not true	0
I dread each coming day	True	1
	Not true	0
I enjoy my food	True	0
	Not true	1
I avoid people if I can	True	1
	Not true	0
I am reluctant to answer the door or the telephone	True	1
	Not true	0
My life has no meaning	True	1
	Not true	0
I am able to cope with everyday problems	True	0
	Not true	1

VENTURA-LT**7. REFERENCES**

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