Official Title: A 52-Week Open-Label Extension Study of Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment

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STATISTICAL ANALYSIS PLAN

Protocol No.:	ACP-103-055
Protocol Title:	A 52-Week Open-Label Extension Study of Pimavanserin in Subjects With Major Depressive Disorder and Inadequate Response to Antidepressant Treatment
Drug:	Pimavanserin
Sponsor:	Acadia Pharmaceuticals Inc. [redacted]
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ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CGI-S	Clinical Global Impression scale – Severity
COVID-19	Coronavirus disease 2019
CSFQ-14	Changes in Sexual Functioning Questionnaire Short Form
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
ESRS-A	Extrapyramidal Symptom Rating Scale–Abbreviated
ET	Early Termination
GSD	Guidance for Site Documentation and Data Management Querying of Data Impacted by COVID-19
HAMD-17	Hamilton Depression Scale (17 items)
MedDRA	Medical Dictionary for Regulatory Activities
msec	milliseconds
OL	open-label
PCI	potentially clinically important
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis System
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

1 INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety and efficacy data as described in the study protocol Amendment 4 dated 11 August 2020. Specifications for tables, figures, and listings are contained in a separate document.

2 OBJECTIVES

2.1 Primary Objective

- To assess the safety and tolerability of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment

2.2 Exploratory Objectives

- To explore the safety and tolerability of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment on the following:
    - suicidality
    - extrapyramidal symptoms
    - general health assessments
- To explore the benefits of long-term pimavanserin treatment in subjects with major depressive disorder and inadequate response to antidepressant treatment on the following:
    - improvement of depression symptoms
    - clinical global impression of severity of depressive symptoms
    - functional impairment
    - sexual functioning

3 STUDY DESIGN

3.1 General Study Design

This study is an open-label extension study to evaluate the long-term safety and tolerability of pimavanserin in subjects with major depressive disorder and inadequate response to antidepressant treatment. This study will be conducted as a 52-week extension of Studies ACP-103-054, and -059.

Subjects who have completed Studies ACP-103-054, or -059, who continue to meet entry criteria, and who may continue to benefit from adjunctive pimavanserin treatment based on the Investigator's judgment will be included in this long-term extension study.

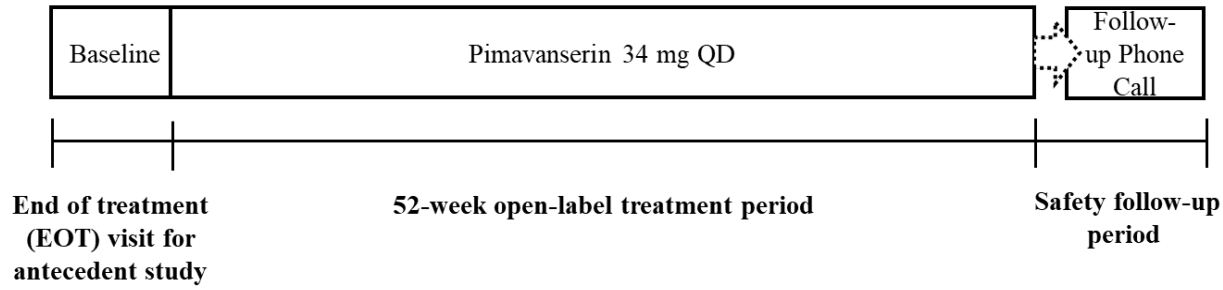
All subjects will receive pimavanserin once-daily dosing at 34 mg over 52 weeks of treatment. During the treatment period, clinic visits will be conducted at Baseline and Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT), or upon early termination (ET) from the study.

Study drug will be dispensed to the subject to take home at the Baseline visit and at Weeks 4, 8, 12, 16, 28, and 40. The subject will be instructed to take the first dose of study drug on the day after the Baseline visit. It is recommended that the subject should take the study drug at approximately the same time each day.

A 30-day safety follow-up telephone contact is to be completed for subjects who complete the treatment period of the study, as well as those who discontinue prematurely from the study.

Figure 1 illustrates the study design.

Figure 1 Schematic of Study Design



Abbreviation: QD=once daily
Note: The antecedent study is either Study ACP-103-054 or Study ACP-103-059.

3.2 Schedule of Assessments

Schedule of events and assessments can be found in Appendix A.

3.3 Randomization

Not applicable.

3.4 Blinding

Not applicable.

3.5 Determination of Sample Size

It is estimated that approximately 420 subjects from Study ACP-103-054 and Study ACP-103-059 will be eligible to enter this study. The sample size for this study is not based on statistical power, but will depend on the number of subjects who transition into this open-label extension study from the antecedent studies, Study ACP-103-054 and Study ACP-103-059.

ACP-103-054, -059 and -055 were stopped early; the estimated number of subjects will be less than originally estimated.

3.6 Coronavirus Disease 2019

In March, 2020, the emerging coronavirus disease 2019 (COVID-19) pandemic resulted in implementation of urgent safety measures designed to ensure subject safety. Mechanisms to record information on the potential impact of the COVID-19 pandemic on data itself, as well as data collection and integrity, were implemented (as detailed in the "Guidance for Site Documentation and Data Management Querying of Data Impacted by COVID-19" [GSD] in the Data Management Plan).

Screening and enrollment into studies ACP-103-054 and ACP-103-059 were closed and enrollment into ACP-103-055 was allowed to continue. The impact of COVID-19 on the statistical analysis is discussed in each of the relevant sections of this SAP.

Subjects who remained in this study who could not attend clinic visits were allowed to participate in remote visits via telephone or video, or site staff conducted the visit in a subject's home. Sites were required to document details of all visits that are administered remotely.

Afterwards, ACP-103-055 was stopped early and the remaining subjects were discontinued in the study.

4 ANALYSIS SETS

The Safety Analysis Set will consist of all enrolled subjects who have taken at least one dose of open-label study drug. The Safety Analysis Set will be used for all analyses.

5 DATA HANDLING CONVENTIONS

All data collected in the study will be listed.

5.1 General Data Reporting Conventions

For continuous variables, the following summary statistics will be provided: number of subjects, mean, standard error of the mean (SE), standard deviation (SD), minimum, maximum, and median. Unless specified otherwise, means, and medians will be presented to one more decimal place than the raw data, and the SDs and SEs will be presented to 2 more decimal places than the raw data.

For categorical variables, summaries will include the number and percentage of subjects in each category, using the number of subjects with non-missing values as the denominator for the percentages (unless otherwise specified). Categories with zero counts will not have zero percentages displayed. Percentages will be presented to 1 decimal place.

When converting number of days to months, it will be calculated as the number of days divided by 365.25 and then multiplied by 12. When converting number of days to years, it will be calculated as the number of days divided by 365.25.

No hypothesis testing is planned. Descriptive summaries of all safety and efficacy endpoints will be provided.
All safety and efficacy endpoints will be summarized for the Safety Analysis Set. In addition, summaries by treatment group according to the original double–blinded treatment actually received in the antecedent study (placebo or pimavanserin) will also be provided.
For each continuous measure in safety and efficacy analyses, change from Baseline results will be presented in two ways:

1. Main analysis: using the Baseline from Study ACP-103-055 and reporting the changes across Study ACP-103-055 timepoints
2. Exploratory analysis: using the Baseline from the antecedent study (ACP-103-054 or ACP-103-059), and reporting the changes across Study ACP-103-055 timepoints

For the treatment responder rate, the summary will also be presented in two ways:

1. Main analysis: using the Baseline from Study ACP-103-055 and reporting the rate across Study ACP-103-055 timepoints
2. Exploratory analysis: using the Baseline from the antecedent study (ACP-103-054 or ACP-103-059), and reporting the rate across Study ACP-103-055 timepoints

The treatment remission rate and the percentage of subjects with sexual dysfunction will also be summarized across Study ACP-103-055 timepoints using the Baseline from Study ACP-103-055 and the Baseline from the antecedent double-blind studies as reference points.

5.2 Derived Variables

In general, the assessment scale total scores and subscores will be derived within the analysis datasets. In the event that total scores and/or subscores are also collected on the electronic case report form (eCRF), the derived values will be used for all analyses. Both the raw and derived scores will be presented in listings.

5.2.1 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT/ET). C-SSRS is a safety assessment and subjects rolled over from all antecedent studies will be assessed.

The C-SSRS version assessing information since the last visit will be completed at all visits (including the Baseline visit).

There are 5 questions about suicidal ideation, representing 5 types of suicidal ideation: wish to be dead; non-specific active suicidal thoughts; active suicidal ideation with any methods (not plan) without intent to act; active suicidal ideation with some intent to act, without specific plan; active suicidal ideation with specific plan and intent. If a subject answers “yes” to any of these 5 questions, this subject will be counted as having suicidal ideation.

There are 5 questions about suicidal behavior, representing 5 types of suicidal behavior: preparatory acts or behavior; aborted attempt; interrupted attempt; actual attempt; suicide. If a subject answers “yes” to any of these 5 questions, this subject will be counted as having suicidal behavior.

Suicidality is defined as a subject who reported at least 1 occurrence of suicidal ideation or at least 1 occurrence of suicidal behavior at any post-Baseline visit including unscheduled and out of window visits.

Missing C-SSRS item scores will not be imputed.

5.2.2 Extrapyramidal Symptom Rating Scale–Abbreviated (ESRS-A)

The ESRS-A is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT/ET). The ESRS was developed to assess drug induced movement disorders such as parkinsonism, akathisia, dystonia and tardive dyskinesia with established reliability, validity, and sensitivity. The ESRS-A, an accepted modified form of the original ESRS, is used during the study to monitor for any worsening in extrapyramidal symptoms or signs at scheduled and

unscheduled visits. The CGI-S for each movement subtype (i.e., parkinsonism, dystonia, dyskinesia, and akathisia) rates the severity of a subject's movement disorder and the CGI-S score for each movement subtype ranges from 0 to 5:

0 = Absent 1 = Minimal 2 = Mild

3 = Moderate 4 = Severe 5 = Extreme

Higher CGI-S scores denote more severe movement disorder. Missing scores will not be imputed.

5.2.3 Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14)

The CSFQ-14 is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT/ET). The CSFQ-14 is a 14-item version of the CSFQ. This is a patient-facing questionnaire, with a male version and a female version. The total score ranging from 14 to 70 will be calculated as the sum of the scores for all 14 items. Higher total scores denote better sexual functioning. Missing item scores will be imputed using the arithmetic mean of the non-missing item scores and rounded to the nearest integer. The total score will be considered as missing if there are missing scores for 3 or more items.

5.2.4 Clinical Global Impressions Scale – Severity (CGI-S)

The CGI-S is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT/ET). The CGI-S is the scale used by the Investigator or designee to rate the severity of the disorder. The CGI-S rates the severity of a subject's depression over the past 7 days and the CGI-S score ranges from 1 to 7:

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

Higher CGI-S scores denote more severe depression. Missing CGI-S scores will not be imputed.

5.2.5 Hamilton Rating Scale for Depression – 17 Items

The HAMD-17 is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT/ET). The HAMD-17 consists of 8 items with a score on a 3 point scale and 9 items with a score on a 5 point scale. The total score ranging from 0 to 52 will be calculated as the sum of the scores

for all 17 items. Higher total scores denote more severe depression. Missing item scores will be imputed and rounded to the nearest integer as follows:

- Missing scores for items with a score on a 3 point scale will be imputed using the arithmetic mean of the non-missing scores for items with a score on a 3 point scale
- Missing scores for items with a score on a 5 point scale will be imputed using the arithmetic mean of the non-missing scores for items with a score on a 5 point scale

The total score will be considered as missing if there are missing scores for 4 or more items.

5.2.6 Sheehan Disability Scale (SDS)

The SDS is assessed at Baseline, Weeks 4, 12, 28, and 52 (EOT/ET). The SDS is a 3-item subject-facing questionnaire used to evaluate impairments in the domains of work, social life/leisure, and family life/home responsibility. Subjects rate each item using an 11-point scale ranging from 0 (not at all) to 10 (extremely).

The primary analysis will be performed on the mean score ranging from 0 to 10 calculated as the arithmetic mean of the scores for all 3 items and rounded to the nearest 2 decimal places. Higher mean scores denote greater disability. If a subject indicates that no work/school occurred, the mean score will be calculated as the arithmetic mean of the other two item responses (Social Life and Family Life/Home Responsibilities) and rounded to the nearest 2 decimal places. If either of the other two item responses is missing, or if the work/school response is missing and the subject does not indicate that no work/school occurred, the mean score will be missing.

5.2.7 Karolinska Sleepiness Scale (KSS)

The KSS is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT/ET). The KSS is a scale that measures the subject's drowsiness and is frequently used in studies measuring subjective sleepiness. Scoring is based on a 9-point verbally anchored scale going from "1 = extremely alert" to "9 = very sleepy, great effort to keep awake, fighting sleep". Higher scores denote more drowsiness. Missing scores will not be imputed.

5.3 Analysis Visit Windows

In general, the open-label Baseline assessment will be defined as the last non-missing assessment, including those from repeated and unscheduled measurements, before or on the first open-label dose date. Exceptions to this definition will be handled on a case by case basis.

Efficacy and safety assessments will be summarized by analysis visit as presented in Table 1 below.

Table 1 Analysis Visit Windows

Open-label (OL) Analysis Visit Name	Target Study Day[1]	Study Day Interval
OL Baseline	1	≤1 (based on the first OL dose date)
OL Week 2	15	2 to 21
OL Week 4	29	22 to 42
OL Week 8	57	43 to 70
OL Week 12	85	71 to 98
OL Week 16	113	99 to 154
OL Week 28	197	155 to 238
OL Week 40	281	239 to 322
OL Week 52	365	323 to 379
OL Follow-up	395	380 – maximum

[1] If the assessment date ≥ first OL dose date, study day = assessment date - first OL dose date + 1, otherwise study day = assessment date – first OL dose. Study day 1 is the first OL dose date.

5.3.1 Unscheduled Assessments

Both scheduled and unscheduled assessments, including early termination visits and remote visits, will be considered for planned timepoint summaries. All assessments will be presented in data listings.

5.3.2 Multiple Measurements within Visit Windows

If more than one assessment falls within a given window then the assessment closest to the target study day will be selected for the by-visit summaries. If two assessments are equidistant from the target day then the chronologically last assessment will be used for summary. Exceptions may be made for incomplete assessments, in which case, more complete assessments may be given priority. Details are provided in a separate programming conventions document.

For safety summaries where the most extreme values should be selected, e.g. overall post-baseline minimum, overall post-baseline maximum, and potentially clinically important values for overall post-Baseline summaries, all non-missing post-Baseline values should be considered, regardless of whether the value is selected for the by-visit summaries. All results will be presented in data listings.

5.4 Data Handling Conventions

5.4.1 Missing or Incomplete Date for Last Dose of Study Drug

In the Safety Analysis Set, if the last dose date of study drug is missing for a subject who completed or early terminated from the study, then the missing last dose date of study drug will be imputed using the last expected dosing date or EOT/ET date, whichever occurs earlier. The last expected dosing date will be calculated as the last drug dispense date plus the expected dosing interval days. For the incomplete last dose date of the study drug, the imputation algorithms will be detailed in the analysis dataset specification document. The missing or incomplete dates will be displayed in the data listings as reported on the eCRF rather than the imputed dates.

For the data summarization before final database lock, if a subject is still ongoing, then this subject's last dose date will be imputed using the database extract date.

5.4.2 Missing or Incomplete Dates for Concomitant or Post-Treatment Medications

Missing or incomplete medication start or end dates will be imputed for the purpose of determining whether the medications are taken concomitantly (see Section 11 for definition). When the chronological order of medication use relative to the study drug treatment period is unclear due to missing or incomplete date(s), the medication will be considered as concomitant. The imputation algorithms will be detailed in the analysis dataset specification document. The missing or incomplete dates will be displayed in the data listings as reported on the eCRF rather than the imputed dates.

5.4.3 Missing or Incomplete Dates for Adverse Events

Missing or incomplete adverse event (AE) start dates will be imputed for the purpose of determining whether the AEs are treatment-emergent (see Section 14.1 for definition). When the chronological order of an AE onset relative to the study drug treatment period is unclear due to missing or incomplete date(s), the AE will be considered as treatment-emergent. The imputation algorithms will be detailed in the analysis dataset specification document. The missing or incomplete dates will be displayed in the data listings as reported on the eCRF rather than the imputed dates.

5.4.4 Missing Severity Assessment for Adverse Events

If the severity is missing for a treatment-emergent AE, a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, and the actual values will be presented in data listings.

5.4.5 Missing Relationship to Study Drug for Adverse Events

If the relationship to study drug is missing for a treatment-emergent AE, a causality of "Related" will be assigned. The imputed values for relationship to study drug will be used for incidence summaries, and the actual values will be presented in data listings.

5.4.6 Character Values of Clinical Laboratory Variables

If the reported value of a clinical laboratory variable cannot be used in a summary due to, for example, a character string reported for a numeric variable, an appropriately determined coded value will be used in the summary. The coding algorithms will be detailed in the analysis dataset specification document. The actual values as reported in the database will be presented in data listings.

6 SUBJECT DISPOSITION

The number of sites that evaluated at least one subject for enrollment and number of subjects enrolled will be summarized by study (ACP-103-054 and ACP-103-059) and overall. Enrolled subjects are subjects who signed informed consent for Study ACP-103-055 and not recorded as "rollover failure" on eCRF.

For enrolled subjects, number and percentage of subjects in the Safety Analysis Set will be summarized. A listing will be provided displaying all subjects excluded from the Safety Analysis Set (if any), and will include reason(s) for exclusion.

The number and percentage of subjects in the Safety Analysis Set who completed the study or discontinued (all discontinued and by discontinuation reasons including the reasons due to COVID-19) will also be summarized. Summaries by study (ACP-103-054 and ACP-103-059) will also be presented.

7 PROTOCOL DEVIATIONS

Protocol deviations that occurred during the extension study period will be reviewed periodically over the course of the study. The review process, definition of the deviation categories, and the classification of a deviation as major or minor are detailed in the Protocol Deviation Management Plan. Protocol deviations will also be assessed with respect to relationship to COVID-19.

For enrolled subjects, a summary of the number and percentage of subjects with major protocol deviations for each deviation category will be presented in three ways: all protocol deviations, COVID-19 related protocol deviations, and non COVID-19 related protocol deviations.

Two listings of major protocol deviations will be provided: all deviations and non COVID-19 related protocol deviations. A listing of all COVID-19 related protocol deviations including the major and the minor will be provided.

8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics and open-label Baseline characteristics will be summarized for the Safety Analysis Set using descriptive statistics. Summaries by study (ACP-103-054 and ACP-103-059) will also be presented. Variables include age, age group (18-40 years and >40 years), sex, primary race, ethnicity, height, weight, body mass index (BMI), antecedent study (ACP-103-054 and ACP-103-059), Baseline HAMD-17 total score, Baseline HAMD-17 total score <24 and ≥24, Baseline CGI-S, Baseline SDS mean score, Baseline CSFQ-14 total score, Baseline KSS score, and antidepressant (SSRI and SNRI).

Race will also be categorized by White vs. Non-White. The eCRF reported age reflects a subject's age at the open-label Baseline visit date. Baseline CGI-S will be summarized as both a continuous variable and a categorical variable.

Depression history will be summarized for Safety Analysis Set using descriptive statistics. Variables include:

- Age at first onset of depression symptoms (years)
- Age at MDD diagnosis (years)
- Number of depression episodes during the subject's lifetime
    - Summary statistics for both the continuous variable and the categorical variable (1 to 5 and ≥6)
- Number of hospitalizations for depression during the subject's lifetime
    - Summary statistics for both the continuous variable and the categorical variable (0; 1 to 5; and ≥6)
- Duration of the current episode of depression (months relative to the open-label Baseline visit date)

Depression history as described above, date of last hospitalization (if number of hospitalizations is greater than 0), and onset date for the current episode of depression will also be presented in a data listing.

9 MEDICAL HISTORY

Medical history data will be coded using Medical Dictionary for Regulatory activities (MedDRA) version 23.0. The subject incidence will be summarized for each system organ class (SOC) and preferred term for the Safety Analysis Set. A subject will be counted only once per SOC or per preferred term for the summary.

A listing of the SOC, preferred term, body system, verbatim term for the medical history condition/event, start and stop dates (when available), and an indicator for whether or not the condition is ongoing will be provided.

10 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

Summaries of exposure and compliance to study drug will be provided for the Safety Analysis Set.

10.1 Exposure to Study Drug

10.1.1 Exposure to Open-label Pimavanserin

For each subject, the duration of exposure to open-label pimavanserin (open-label last dose date – open-label first dose date + 1) will be calculated and summarized. The number and percentage of subjects within each of the following exposure levels in terms of duration of exposure will also be tabulated: <2 week (1 to 13 days), 2 to <4 weeks (14 to 27 days), 4 to <8 weeks (28 to 55 days), 8 to <12 weeks (56 to 83 days), 12 to <16 weeks (84 to 111 days), 16 to <28 weeks (112 to 195 days), 28 to <40 weeks (196 to 279 days), 40 to <52 weeks (280 to 363 days), ≥52 weeks (≥364 days).

In addition, the maximum dose in the open-label period, final dose in open-label period, and the mean daily dose during open-label period will be determined for each subject and summarized. The mean daily dose will be calculated as the number of pimavanserin tablets taken in the open label period multiplied by 17 (mg) divided by the duration of total exposure in the open-label period in days.

10.1.2 Total Exposure to Pimavanserin Across the Double-blind and Open-label Periods

For subjects who received pimavanserin in the antecedent studies, the total duration of exposure (in days) to pimavanserin will be calculated as the sum of the exposure durations in the double-blind and open-label periods:

$$[(\textit{date of last double-blind dose}) - (\textit{date of first double-blind dose}) + 1] + [(\textit{date of last open-label dose}) - (\textit{date of first open-label dose}) + 1].$$

In case that a subject whose last dose date in the antecedent study is equal the first dose date in the extension study, the total duration of exposure (in days) to pimavanserin will be the exposure durations in the double-blind and open-label periods minus one (i.e. the above formula minus one). For subjects who received placebo in the antecedent studies, the total duration of exposure to pimavanserin across the double-blind and open-label periods will be the same as the values calculated for the open-label study period alone. Duration of total exposure across the double-blind and open-label periods will be summarized descriptively.

Duration of total exposure will also be tabulated as a categorical variable: <2 week (1 to 13 days), 2 to <4 weeks (14 to 27 days), 4 to <8 weeks (28 to 55 days), 8 to <12 weeks (56 to 83 days), 12 to <16 weeks (84 to 111 days), 16 to <28 weeks (112 to 195 days), 28 to <40 weeks (196 to 279 days), 40 to <52 weeks (280 to 363 days), 52 to <54 weeks (364 to 377 days), 54 to <56 weeks (378 to 391 days), 56 to <57 weeks (392 to 398 days), and ≥57 weeks (≥399 days).

In addition, the maximum dose across the double-blind and open-label periods and the mean daily dose across the double-blind and open-label periods will be determined for each subject and summarized. The mean daily dose will be calculated as the number of pimavanserin tablets taken across the double-blind and open-label periods multiplied by 17 (mg) divided by the duration of total exposure across the double-blind and open-label periods in days.

10.2 Measurement of Treatment Compliance

Study drug dosing compliance (in percentage) during the open-label study period for a subject is defined as:

$$\frac{(total\ number\ of\ tablets\ actually\ taken)}{(total\ number\ of\ tablets\ expected\ to\ be\ taken)} \times 100.$$

The total number of tablets actually taken is calculated as:

(*the total number of tablets dispensed*) – (*the total number of tablets returned*).

The total number of tablets expected to be taken is calculated as:

(*the duration of exposure*) × 2.

For any visit with unreturned drug kits, the total number of tablets actually taken will be imputed as the total number of tablets expected to be taken for that visit period.

Compliance will be summarized as both continuous and categorical variables. For categorical presentation, the number and percentage of subjects in each of the following categories will be presented: <80%, 80 to 120%, and >120%.

11 CONCOMITANT AND POST-TREATMENT MEDICATION

Concomitant medication is defined as any medication with a start date prior to the date of the open-label first dose and continuing after the open-label first dose date or with a start date between the open-label first dose date and open-label last dose date, inclusive. Any medication with a start date after the open-label last dose date will be considered as post-treatment medication. Concomitant and post-treatment medications will be summarized separately. Relationship to COVID-19 will be assessed for selected medications as detailed in the GSD. Concomitant and post-treatment medication analyses described above will also be

summarized by relationship to COVID-19 (Not related to COVID-19 vs. Related to COVID-19).

Medications will be coded using WHO Drug Dictionary March 2020. For concomitant medications, the number and percentage of subjects taking each drug class (ATC Level 3) and medication preferred term will be tabulated for Safety Analysis Set. A subject will be counted only once per drug class or per medication preferred term for the summary.

12 EFFICACY ANALYSES

All efficacy analyses will be performed for the Safety Analysis Set. No hypothesis testing is planned. Descriptive summaries of all efficacy endpoints will be provided.

12.1 Efficacy Variables

Efficacy Endpoints

- Change from Baseline in Hamilton Depression Scale (17 items) (HAMD-17) total score
- Treatment responder rates. Treatment response is defined as a reduction from Baseline in HAMD-17 total score of 50% or more.
- Treatment remission rates. Treatment remission is defined as a HAMD-17 total score ≤7.
- Change from Baseline in Clinical Global Impression–Severity (CGI-S) score for depressive symptoms
- Change from Baseline in Sheehan Disability Scale (SDS) mean score
- Change from Baseline in the Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14) total score
- Change from Baseline in Karolinska Sleepiness Scale (KSS) score

12.2 Adjustment for Covariates

Not applicable.

12.3 Handling of Missing Data

Any derived scores (i.e. total, domain, or subscale scores) that are missing, after the imputation of individual missing items as described in Section 5.2, will not be imputed.

12.4 Multiple Comparisons / Multiplicity

No hypothesis testing is planned.

12.5 Examination of Subgroups

Summaries for below subgroups will be tabulated for the change from Baseline in the HAMD-17 total score, the SDS mean score, the CGI-S score, the CSFQ-14 score, and the KSS score:

- age group (18-40 years and >40 years)
- sex (male and female)
- background antidepressant type (SSRI [citalopram, escitalopram, paroxetine, fluoxetine, or sertraline] and SNRI [duloxetine, venlafaxine, desvenlafaxine, or venlafaxine XR])

13 METHODS OF EFFICACY ANALYSES

Descriptive statistics for all efficacy endpoints listed in Section 12.1 including treatment responder and remission rates will be tabulated by the double-blind treatment group in the antecedent studies at scheduled timepoints. The summaries of the change from Baseline results will be presented in two ways (main analysis and exploratory analysis) as specified in Section 5.1.

14 SAFETY ANALYSES

The safety summaries will be presented for the Safety Analysis Set using descriptive statistics. Safety variables include AEs, clinical laboratory variables, vital signs, body weight, BMI, physical examinations, ECG, C-SSRS, ESRS-A, and sexual dysfunction defined as a CSFQ-14 total score of ≤47 for men and ≤41 for women. Safety variables will also be summarized by the double-blind treatment group in the antecedent studies. For each continuous measure in clinical laboratory variables, vital signs, and electrocardiogram, change from Baseline results will be presented in two ways (main analysis and exploratory analysis) as specified in Section 5.1.

14.1 Adverse Events

An AE is considered as treatment-emergent adverse event (TEAE) if it started on or after the open-label first study dose date and no later than the open-label last study dose date + 30 days.

The event counts and the number and percentage of subjects reporting TEAEs will be tabulated by SOC and preferred term; and, by SOC, preferred term, and maximum severity. If more than 1 AE occurs with the same preferred term for the same subject, the subject will be counted only once for that preferred term using the most severe occurrence for the summarization by severity. In addition, the event counts and the number and percentage of subjects with TEAEs classified by the Investigators as related to the study drug, with most

frequently reported TEAEs (preferred terms reported by ≥5% of subjects in the Safety Analysis Set), with treatment-emergent serious AEs (TESAEs), with fatal AEs (i.e. events that cause death), and with TEAEs leading to discontinuation of study drug will be summarized by SOC and preferred term. The display in these tables will be sorted alphabetically by SOC and then by descending subject frequency for the preferred terms (based on counts in the Safety Analysis set) within each SOC.

The relationship of selected AEs to COVID-19 will be assessed as detailed in the GSD. TEAEs tabulated by SOC and preferred term will be presented three ways: all TEAE, COVID-19 related TEAE, and not COVID-19 related TEAE.

The event counts and the number and percentage of subjects with any TEAEs will also be tabulated by preferred term without SOCs. The display in this table will be sorted by descending subject frequency based on counts in the Safety Analysis set.

An AE listing by subject will display all events, including those which are not treatment-emergent, and will include the verbatim term in addition to the MedDRA SOC and preferred term. This listing will also include all relevant eCRF data associated with the event: e.g. date of onset, date resolved, date of the open-label first dose, date of the open-label last dose, dose level at AE onset, severity, frequency, outcome, relationship to study drug, action taken with study drug, and required therapy. When a date is presented, the study day associated with the date will also be displayed. Separate listings will be presented for subjects with SAEs, subjects with AEs leading to discontinuation and subjects who died (if any), and subjects with all COVID-19 related AEs.

14.2 Clinical Laboratory Variables

Clinical laboratory tests are performed at Baseline, Week 12, and Week 52 (EOT/ET).

In general, laboratory test results are from a central laboratory. Due to COVID-19 disruptions it is possible that some test results may be collected from a local laboratory. A separate eCRF will capture local laboratory results in order to facilitate medical monitoring of subject safety. Local laboratory results will not be included in any summary data analysis; they will, however, be included in separate data listings. All results (central and local) will be displayed in Système International [SI] units. It is encouraged, but not required, that clinical labs be completed under fasting conditions. The listings will include date and study day of collection. Out of range values will be flagged in the data listings.

- Hematology tests
  - Complete blood count (CBC) including:
    - White blood cell (WBC) count
    - Complete differential (relative and absolute)
    - Hematocrit (Hct), hemoglobin (Hgb), red blood cells (RBC), platelets
    - Reticulocyte count
- Clinical chemistry serum tests
  - Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca), carbon dioxide (CO_2), blood urea nitrogen (BUN), creatinine (Cr), uric acid
  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
  - Glucose
  - Albumin (ALB), total protein
  - Prolactin
  - Creatine kinase (CK)/creatine phosphokinase (CPK)
  - Lipid panel
    - Total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, low-density lipoprotein(LDL)-cholesterol, very low density lipoprotein cholesterol
- Urinalysis
  - Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH

Clinical laboratory values reported as continuous values for hematology, chemistry and urinalysis will be summarized using descriptive statistics at Baseline and scheduled post-Baseline visits. The change from Baseline values will also be summarized at scheduled post-Baseline visits. The overall minimum, maximum and last post-Baseline observed and change from Baseline values will also be summarized. For hemoglobin, hematocrit and uric acid, the above summaries will be presented for each gender as well as for both genders combined. For urinalysis with categorical results, the number and percentage of subjects will be tabulated by category at Baseline and scheduled post-Baseline visits, and the denominator is the number of subjects with non-missing values for the given parameter and visit. For glucose and lipid panel, the summary table will also be presented by fasting status (fasting vs. non-fasting).

Laboratory values will also be summarized in shift tables to determine the number and percentage of subjects with values classified as below (low), within (normal), or above (high) normal ranges at scheduled post-Baseline visits relative to the same classification at the Baseline visit. The shifts from Baseline to overall post-Baseline minimum and overall post-Baseline maximum will also be presented. For the by-visit shift summary, the denominator is the number of subjects with non-missing values at Baseline and the given visit for the given

parameter. For the summaries of shift from Baseline to the overall post-Baseline minimum or maximum, the denominator is the number of subjects with non-missing Baseline and at least 1 post-Baseline value for the given parameter. For hemoglobin, hematocrit and uric acid, the shift summaries will be presented for each gender as well as for both genders combined. For glucose and lipid panel, the shift table will be presented by fasting status (fasting vs. non-fasting).

Number and percentage of subjects with potentially clinically important (PCI) laboratory values at scheduled post-Baseline visits and overall post-Baseline will be summarized by Baseline status (all or within normal range) for selected parameters. PCI criteria are listed in Table 2 and Table 3. For the overall post-Baseline summaries, all post-Baseline values will be considered, including unscheduled and out of window values. Subjects with multiple PCI values for a given parameter will be counted only once for that parameter. For the by-visit summary, the numerator for the percentage is the number of subjects with a post-Baseline PCI value for the given parameter and visit, and the denominator is the number of subjects with non-missing values for the given parameter and visit. For the overall post-Baseline summary, the numerator for the percentage is the number of subjects with at least 1 post-Baseline PCI value for the given parameter, and the denominator is the number of subjects with at least 1 post-Baseline value for the given parameter. For hemoglobin, hematocrit, and uric acid, the count and percentage of subjects with PCI values will be presented for each gender as well as for both genders combined. A listing of all PCI values in study ACP-103-055 will be provided. This listing will include all observations from study ACP-103-055 for those subjects and parameters for which at least one PCI value (including OL Baseline) was observed.

Table 2 Criteria for Potentially Clinically Important Laboratory Values – Hematology and Chemistry

Analyte	Conventional Unit	Low PCI Criteria	High PCI Criteria	SI Unit	Low PCI Criteria	High PCI Criteria
Hematology (whole blood)						
Hemoglobin (male)	g/dL	<11	>18	g/L	<110	>180
Hemoglobin (female)	g/dL	<10	>17	g/L	<100	>170
Hematocrit (male)	%	<30	>55	L/L	<0.3	>0.55
Hematocrit (female)	%	<30	>50	L/L	<0.3	>0.5
Leukocyte (White Blood Cell Count)	x 10^3/uL	≤2.8	≥15	x 10^9/L	≤2.8	≥15
Neutrophils	x 10^3/uL	≤1.5	No upper limit	x 10^9/L	≤1.5	No upper limit
Platelet Count	x 10^3/uL	≤75	≥700	10^9/L	≤75	≥700
Chemistry (serum or plasma)						
ALT (SGPT)	U/L	No lower limit	≥3 X ULN	U/L	No lower limit	≥3 X ULN
AST (SGOT)	U/L	No lower limit	≥3 X ULN	U/L	No lower limit	≥3 X ULN
Total Bilirubin	mg/dL	No lower limit	≥1.5 ULN	umol/L	No lower limit	≥1.5 ULN
BUN	mg/dL	No lower limit	≥30.0	mmol/L	No lower limit	≥10.71
Creatine Kinase (CK)	U/L	No lower limit	≥3 ULN	U/L	No lower limit	≥3 ULN
Sodium	mEq/L	≤125	≥155	mmol/L	≤125	≥155
Potassium	mEq/L	≤3.0	≥5.5	mmol/L	≤3.0	≥5.5
Calcium, total	mg/dL	<8.0	>11.0	mmol/L	<2.0	>2.75
Lactate Dehydrogenase (LDH)	U/L	No lower limit	≥3 X ULN	U/L	No lower limit	≥3 X ULN
Alkaline Phosphatase	U/L	No lower limit	≥3 X ULN	U/L	No lower limit	≥3 X ULN
Uric acid (male)	mg/dL	No lower limit	≥10.5	umol/L	No lower limit	≥624.75
Uric acid (female)	mg/dL	No lower limit	≥8.5	umol/L	No lower limit	≥505.75
Albumin	g/dL	≤2.6	≥6.0	g/L	≤26	≥60
Total Protein	g/dL	≤5.0	≥10.0	g/L	≤50	≥100
Chloride	mEq/L	≤85	≥120	mmol/L	≤85	≥120
Glucose (random)	mg/dL	≤45.1	≥200.0	mmol/L	≤2.48	≥11
Serum Creatinine	mg/dL	Not Applicable	>1.5 ULN	umol/L	Not Applicable	>1.5 ULN
Triglycerides	mg/dL	Not Applicable	>300	mmol/L	Not Applicable	>3.39
Gamma-Glutamyl Transferase (GGT)	U/L	Not Applicable	≥3 ULN	U/L	Not Applicable	≥3 ULN

Table 3 Criteria for Potentially Clinically Important Laboratory Values - Urinalysis

Urinalysis (qualitative dipstick)	Low PCI Criteria	High PCI Criteria
Blood (occult blood)	Not Applicable	≥ Moderate
Protein	Not Applicable	≥ 100 mg/dL
Glucose	Not Applicable	≥ 500 mg/dL

The number and percentage of subjects with the shift from baseline, both double-blind and open-label, to weeks 12 and 52 that meet the following criteria in the blood lipid parameters and glucose will be summarized by fasting status (fasting vs. non-fasting):

- Total Cholesterol – (<200 mg/dL to ≥240 mg/dL)
- Triglycerides – (<150 mg/dL to ≥200 mg/dL)
- LDL Cholesterol – (<100 mg/dL to ≥160 mg/dL)
- HDL Cholesterol – (≥40 mg/dL to <40 mg/dL)
- Glucose fasting – (<100 mg/dL to ≥126 mg/dL)
- Glucose non-fasting – (<140 mg/dL to ≥140 mg/dL)
- Glucose fasting – (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)
- Glucose non-fasting - (≥140mg/dL and <200 mg/dL to ≥200 mg/dL)

The pregnancy results (positive or negative) for female subjects will be presented in a listing.

14.3 Vital Signs

Vital signs are assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and 52 (EOT/ET).

Vital signs including weight, height (measured at the screening visit of antecedent studies), and the derived BMI will be summarized using descriptive statistics at Baseline and all scheduled post-Baseline visits. The change from Baseline values will also be summarized at the scheduled post-Baseline visits.

Vital sign values will be considered PCI if they meet the criteria listed in Table 4. The number and percentage of subjects with post-Baseline vital signs that are PCI will be summarized at scheduled post-Baseline visits and for overall post-Baseline. For the overall post-Baseline summaries, all post-Baseline values will be considered, including unscheduled and out of window values. Subjects with multiple PCI values for a given parameter will be counted only once for that parameter. For the by-visit summary, the numerator for the percentage is the number of subjects with a post-Baseline PCI value for the given parameter and visit, and the denominator is the number of subjects with non-missing values for the given parameter and visit. For the overall post-Baseline summary, the numerator for the percentage is the number of subjects with at least 1 post-Baseline PCI value for the given parameter, and the denominator is the number of subjects with at least 1 post-Baseline value

for the given parameter. A listing of all PCI values in study ACP-103-055 will be provided. This listing will include all observations from study ACP-103-055 for those subjects and parameters for which at least one PCI value (including Baseline) was observed.

Table 4 Criteria for Potentially Clinically Important Vital Signs

Vital Sign Parameter	Unit	Criteria[a]		
		Observed Value	And/Or	Change Relative to Baseline
Systolic blood pressure (supine or sitting)	mmHg	≥180	And	Increase of ≥20
		≤90	And	Decrease of ≥20
Diastolic blood pressure (supine or sitting)	mmHg	≥105	And	Increase of ≥15
		≤50	And	Decrease of ≥15
Pulse (supine or sitting)	bpm	≥120	And	Increase of ≥15
		≤50	And	Decrease of ≥15
Weight	kg	Not Applicable		Increase of ≥7%
				Decrease of ≥7%

[a] A post-baseline value is considered as a PCI value if it meets both criteria for observed value and change from baseline.

14.4 Electrocardiogram (ECG)

All tracings will be evaluated by qualified clinicians. At the Baseline visit, the machine-read results will also be recorded. All data, including the machine-read Baseline results, will be listed.

Observed values of ECG variables (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc intervals) and the changes from Baseline at scheduled visits will be summarized.

QTc intervals include QTcB (Bazett's formula) and QTcF (Fridericia's formula). QTcF will also be categorized into the following categories (msec) and the number and percentage of subjects in each category will be summarized at scheduled visits and overall post-baseline maximum:

- Observed: ≤450, 451 - ≤480, 481 - ≤500, and >500; >450; >480.
- Change from Baseline: ≤10, 11 - 30, 31 - 60, and >60; >30.

The above summaries will also be presented for the following subgroups: subjects with background antidepressant of citalopram, subjects with background antidepressant of escitalopram, and subjects with background antidepressant of venlafaxine.

For cardiologist's interpretations, the number and percentage of subjects with ECG results

that are determined as normal or abnormal will be summarized at scheduled visits. The overall post-baseline worst interpretation will also be summarized (i.e. if a subject has one or more ECG results that is/are considered as abnormal, this subject will be counted in the abnormal category). Cardiologist's interpretations will also be summarized in a shift table to determine the number and percentage of subjects with ECG results classified as normal or abnormal at scheduled post-Baseline visits relative to the same classification at the Baseline visit. The shifts from Baseline to overall post-Baseline worst interpretation will also be presented. For the by-visit shift summary, the denominator is the number of subjects with non-missing cardiologist's interpretation at Baseline and the given visit. For the summaries of shift from Baseline to the overall post-Baseline worst interpretation, the denominator is the number of subjects with non-missing Baseline and at least 1 post-Baseline cardiologist's interpretation.

Electrocardiogram values will be considered PCI if they meet or exceed the upper limit values listed in Table 5. The number and percentage of subjects with PCI values will be summarized at scheduled post-Baseline visits and for overall post-Baseline. For the by-visit summary, the numerator for the percentage is the number of subjects with a post-Baseline PCI value for the given parameter and visit, and the denominator is the number of subjects with non-missing values for the given parameter and visit. For the overall post-Baseline summary, the numerator for the percentage is the number of subjects with at least 1 post-Baseline PCI value for the given parameter, and the denominator is the number of subjects with at least 1 post-Baseline value for the given parameter. A listing of all PCI values in study ACP-103-055 will be provided. This listing will include all observations from study ACP-103-055 for those subjects and parameters for which at least one PCI value (including OL Baseline) was observed.

Table 5 Criteria for Potentially Clinically Important ECG Values

ECG Parameter	Unit	High PCI Criteria
QRS Interval	msec	≥120
PR Interval	msec	≥220
QTcB or QTcF	msec	>500
QTcB or QTcF: change from baseline	msec	>60

14.5 Physical Examination

Physical examination is performed at Baseline, Week 28, and Week 52(EOT/ET). Physical examination results (normal, abnormal, and not done) will be summarized at each visit in a frequency table by body system.

14.6 Other Safety Variables

14.6.1 Suicidality Based on C-SSRS

The event counts and the number and percentage of subjects reporting any post double-blind Baseline suicidal ideation, suicidal behavior, or suicidality will be tabulated by the double-blind treatment group in the antecedent studies across the timepoints of both the antecedent study and the open-label Study ACP-103-055. The event counts and the number and percentage of subjects reporting any post-Baseline non-suicidal self-injurious behavior will also be tabulated. For calculating the percentages, the denominator will be the number of subjects in the Safety Analysis Set. In addition, a summary counting of any reports post open-label Baseline will be presented.

14.6.2 CGI-S Score Based on ESRS-A

Descriptive statistics for ESRS-A CGI-S score will be tabulated by the double-blind treatment group in the antecedent studies at scheduled timepoints. The summaries of the change from Baseline results will be presented in two ways (main analysis and exploratory analysis) as specified in Section 5.1.

14.6.3 Sexual Dysfunction Based on CSFQ-14

The number and percentage of subjects with sexual dysfunction defined as a CSFQ-14 total score of ≤47 for men and ≤41 for women will be tabulated by the double-blind treatment group in the antecedent studies across the antecedent study double-blind baseline visit and the open-label Study ACP-103-055 timepoints. For calculating the percentages, the denominator will be the number of subjects in the Safety Analysis Set.

15 CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

16 INTERIM ANALYSIS

One or more interim analyses may be planned in this study to support regulatory submissions.

17 DATA MONITORING/REVIEW COMMITTEE

There is no data monitoring/review committee in this study.

18 COMPUTER METHODS

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® (SAS® Institute, Inc., Cary, North Carolina) on a suitably qualified and validated environment.

Validation and quality control of the tables, listings and figures containing the results of the statistical analyses will follow appropriate standard operating procedures.

19 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

None.

20 REFERENCES

1. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, March 2020; updated May 14, 2020.
2. EMA Guidiance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, March 2020.

21 APPENDICES

Appendix A Schedule of Events and Assessments

Period	Baseline[c]	Treatment Period									Safety Follow-Up[m]
Visit Number	1	2	3	4	5	6	7	8	(EOT/ET) 9		10
Visit Week[a]	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 28	Week 40	Week 52	Unscheduled Visit[l]	Week 56
Type of visit[b]	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
Visit window (# days)		±3	±3	±3	±3	±7	±7	±7	+7		+7
Informed consent and if applicable, privacy forms[c]	X										
Inclusion/exclusion criteria	X										
Medical history, medication history, and demographics[d]	X										
Psychiatric history[d]	X										
Physical examination	X						X		X		
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	
ECG[e]	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests[f]	X				X				X		
Pregnancy test[g]	X		X	X	X	X	X	X	X		
Urine drug screen	X				X				X		
ESRS-A	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	X	X	X	X	X	X	X	X	X	
HAMD-17[h]	X	X	X	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X	X		
SDS	X		X		X		X		X		
CSFQ-14	X	X	X	X	X	X	X	X	X		
KSS	X	X	X	X	X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Assessment of AEs[i]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug	X[j,k]		X	X	X	X	X	X		X[m]	

Period	Baseline[c]	Treatment Period									Safety Follow-Up[m]
Visit Number	1	2	3	4	5	6	7	8	(EOT/ET) 9		10
Visit Week[a]	Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 28	Week 40	Week 52	Unscheduled Visit[l]	Week 56
Study drug accountability	X[k]	X	X	X	X	X	X	X	X	X	
Review of background antidepressant adherence	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: AE=adverse event; CGI-S=Clinical Global Impression–Severity; CSFQ-14=Changes in Sexual Functioning Questionnaire Short Form; C-SSRS=Columbia–Suicide Severity Rating Scale; ECG=electrocardiogram; EOT=end of treatment; ESRS-A=Extrapyramidal Symptom Rating Scale–Abbreviated; ET=early termination; HAMD-17=Hamilton Depression Scale (17 items); KSS=Karolinska Sleepiness Scale; SDS=Sheehan Disability Scale

[a] Study visits are designated by weeks and have a ±3-day window (Visits 2 through 5), or a ±7-day window (Visits 6 through 8), or a +7-day window (Visits 9 and 10), and are calculated from the Baseline Visit.

[b] If visit is performed remotely due to the COVID-19 pandemic, please refer to Sections 3.1.3 (impact of COVID-19 pandemic), 6.2.6 (exploratory efficacy assessments), 6.3.8 (safety assessments) and 6.5.1 (unscheduled visits) of the protocol for further information.

[c] Subject consent for the present study **must be** obtained for entry into the present study prior to the final procedures being performed at the end of treatment (EOT) visit in the antecedent study, Study ACP-103-054 or Study ACP-103-059. Data from the EOT visit procedures of Study ACP-103-054 and Study ACP-103-059 will be carried over as baseline information in the present study, as applicable.

[d] Relevant information collected from Study ACP-103-054 and Study ACP-103-059 will be rolled over to the present study; any updates to this information should be collected during the Baseline visit of the present study.

[e] A single 12-lead ECG can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits. ECGs should be completed with the subject in a supine position after 5 minutes of rest.

[f] To include hematology, serum chemistry, prolactin levels, and urinalysis.

[g] A urine pregnancy test should be performed for female study subjects of childbearing potential. If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place.

[h] The HAMD-17 is to be the first scale completed at each visit.

[i] All ongoing AEs from Study ACP-103-054 and Study ACP-103-059 will be carried over after informed consent has been obtained for the present study and recorded from Baseline for the present study until resolution or the follow-up safety assessment. An AE occurring after the completion of procedures at the EOT visit in Study ACP-103-054 or Study ACP-103-059 will be recorded as an AE in the present study.

[j] Study drug will be dispensed to the subject to take home at the Baseline visit. The subject will be instructed to take the first dose of study drug on the following day.

[k] The used and unused treatment kits, blister cards, and tablets from Study ACP-103-054 and Study ACP-103-059 are to be collected by the Investigator as part of the EOT visit of Study ACP-103-054 and Study ACP-103-059 before study drug for the present study can be dispensed.

[l] At a minimum the safety assessments indicated should be completed at unscheduled visits. Other assessments may be completed at unscheduled visits at the discretion of the Investigator.

[m] Study drug may be dispensed to the subject at unscheduled visits if needed.

[n] This visit is a safety follow-up telephone call visit for subjects who discontinue prematurely from the study or who complete the present study. This visit will occur at least 30 days after the last dose of study drug.

Appendix B Summary of Version Changes

Version No:	Document History Description of Update	Author(s)	Version Date
1.0		[redacted]	11 February 2021