Official Title: A 52-Week Open-Label Extension Study of Pimavanserin in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease

NCT Numbers: NCT03623321

Document Date: 8 March 2021

STATISTICAL ANALYSIS PLAN

Protocol No.:	ACP-103-047
Protocol Title:	A 52-Week Open-Label Extension Study of Pimavanserin in Adult and Elderly Subjects With Neuropsychiatric Symptoms Related to Neurodegenerative Disease
Drug:	Pimavanserin
Sponsor:	Acadia Pharmaceuticals Inc. [redacted]
Version No. and Date:	Version 3.0, 08 March 2021

SIGNATURE/APPROVAL PAGE

AUTHOR

See appended electronic signature page

[redacted]
Director, Biostatistics
Acadia Pharmaceuticals Inc.

Date

APPROVERS

See appended electronic signature page

[redacted]
Vice President, Biometrics
Acadia Pharmaceuticals Inc.

Date

PLACEHOLDER FOR ELECTRONIC SIGNATURE PAGE

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AE	adverse event
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CGI-S	Clinical Global Impression Scale – Severity
COVID-19	coronavirus disease 2019
C-SSRS	Columbia-Suicide Severity Rating Scale
DB	double-blind
DMP	Data Management Plan
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end-of-treatment
EQ-5D-5L	5-level EuroQoL-5D
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
ET	early termination
GCAS	Global Clinical Assessment of Suicidality
IA	interim analysis
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
Msec	Milliseconds
NPI	Neuropsychiatric Inventory
OL	open-label
PCHC	Pareto Classification of Health Change
PCI	potentially clinically important
PT	preferred term
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
SD	standard deviation
SDI	Sleep Disorders Inventory
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
VAS	visual analogue scale

1 INTRODUCTION

This statistical analysis plan provides a technical and detailed elaboration of the statistical analyses of efficacy and safety data as described in the study protocol amendment 4 dated 05 March 2021. Specifications for tables, figures, and listings are contained in a separate document.

For the Czech republic, a country-specific protocol amendment (Amendment 4-CZ dated 23 July 2019) specified additional supervision requirements for subjects with mild, moderate, or severe dementia; added exclusion criteria for tachycardia and blood pressure measurements; and added temperature to list of vital signs assessments.

For Bulgaria, a country-specific protocol amendment (Amendment 3-BG dated 23 July 2019) specified that the designated study partner/caregiver must be in daily contact with the subject. This Amendment also added further details regarding the definitions of prior and concomitant therapies, and clarified the Investigator's options for the use of concomitant medications.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease.

2.1.1 Primary Endpoint

The primary safety measure for this study is treatment-emergent adverse events (TEAEs).

2.2 Secondary Objectives

Not applicable.

2.2.1 Secondary Endpoints

Not applicable.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

- to explore the safety and tolerability of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease on the following:
    - suicidality

- cognition
- extrapyramidal symptoms

- to explore the benefit of long-term pimavanserin treatment in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease on
  - clinical global impression of neuropsychiatric symptoms
  - quality of life
  - sleep

2.3.1 Exploratory Endpoints

The exploratory endpoints to assess the safety and tolerability of long-term treatment pimavanserin are described by:

- Columbia-Suicide Severity Rating Scale (C-SSRS) or Global Clinician Assessment of Suicidality (GCAS) scale (if the subject is not able to complete the C-SSRS in the Investigator's judgement)
- Mini-Mental State Examination (MMSE)
- Extrapyramidal Symptom Rating Scale-Abbreviated (ESRS-A)

Benefits of long-term pimavanserin treatment are described by:

- Change from Baseline in Clinical Global Impression-Severity (CGI-S) score for neuropsychiatric symptoms
- Change from Baseline in the 5-level EuroQol 5D (EQ-5D-5L) score
- Change from Baseline in Sleep Disorder Inventory (SDI) score

3 STUDY DESIGN

3.1 General Study Design

The ACP-103-047 study is a Phase 3b, open-label (OL) extension study to evaluate the long-term safety and tolerability of pimavanserin in adult and elderly subjects with neuropsychiatric symptoms related to neurodegenerative disease. This study will be conducted as a 52-week OL extension of the ACP-103-046 study (antecedent study), consisting of two periods: a 52 week OL treatment period, and a 4 week safety follow-up period. The total duration of exposure to pimavanserin may be greater than 52 weeks as subjects may have been treated with pimavanserin in the antecedent study. Approximately 100 global sites will participate in this study.

Eligible subjects will be those subjects who completed the ACP-103-046 study and, in the Investigator's judgement, may continue to benefit from longer term therapy with pimavanserin. Subject and study partner/caregiver consent for the present study must be obtained prior to the final procedures being performed at the antecedent study's end of treatment (EOT or early termination (ET) visit (if the study was ended early by the Sponsor). Data from the EOT/ET procedures of the antecedent study will be transferred over to the ACP-103-047 study for inclusion as baseline information, and this antecedent EOT visit will be considered the Baseline visit (Visit 1).

Eligible subjects will receive once daily doses of pimavanserin during the treatment period, starting with 34 mg of pimavanserin at the Baseline visit. Dose adjustments of pimavanserin down to 20 mg and up to 34 mg are permitted at any study visit (scheduled or unscheduled) after Baseline.

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 ET from the study.

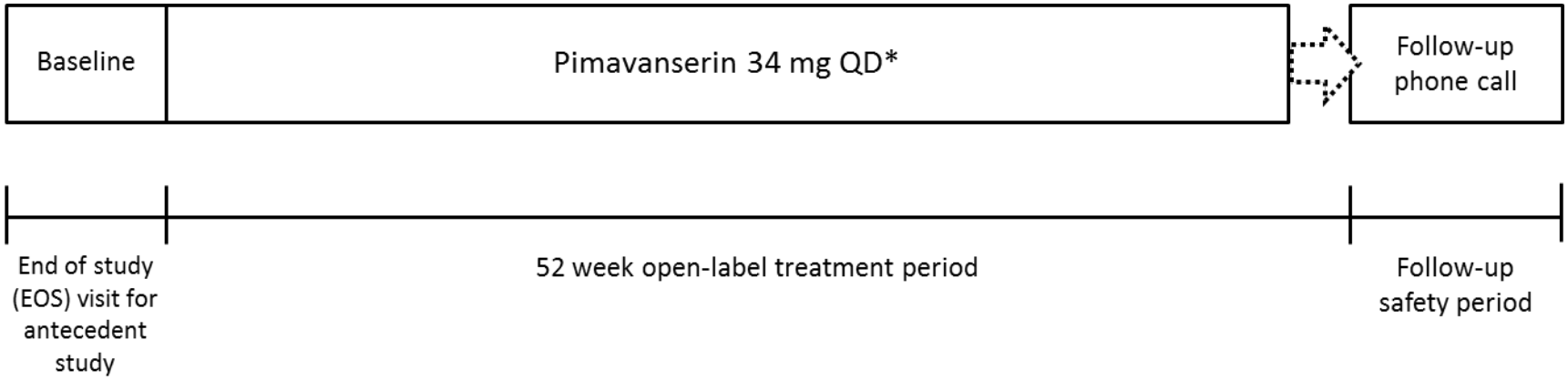
Study drug will be dispensed to the subject to take home at the Baseline visit and at each subsequent visit (with the exception of Week 52). The subject and their study partner/caregiver will be provided instructions to take the first dose of study drug on the day after the Baseline visit. It is recommended that the subject take the study drug at approximately the same time each day as a single, oral dose.

All concomitant permitted medications should remain stable during the study but can be adjusted or discontinued, if clinically appropriate. These changes should be discussed with the Medical Monitor or designee as appropriate.

A safety follow-up telephone call to the subject and study partner/caregiver should at 30 (+4) days after the last dose of study drug.

Figure 1 illustrates the study design.

Figure 1 Schematic of Study Design



* Eligible subjects will begin pimavanserin dosing at 34 mg. Dose adjustments of pimavanserin down to 20 mg and up to 34 mg are permitted at any study visit (scheduled or unscheduled) after Baseline based on Investigator assessment of clinical response.

3.2 Schedule of Assessments

The schedule of events and assessments for the study is presented in Table 1.

Table 1 Schedule of Events and Assessments for ACP-103-047

	Baseline[b]	Treatment Period									Follow-Up[k]
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**	**Week 56**
Type of visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
Allowable visit window (# days)		±3	±3	±3	±3	±7	±7	±7	±7		+4
Informed consent[b]	X										
Inclusion/exclusion criteria	X										
Medical history and demographics	X										
Psychiatric, dementia, and neurological history	X										
Physical examination	X						X		X		
Vital signs	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X		
ECG[c]	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests	X				X				X		
Pregnancy test[d]	X	X	X	X	X	X	X	X	X		
Urine drug screen	X				X				X		
MMSE	X	X	X	X	X	X	X	X	X		
ESRS-A	X	X	X	X	X	X	X	X	X	X	
C-SSRS[e] or GCAS[e]	X	X	X	X	X	X	X	X	X	X	
CGI-S	X	X	X	X	X	X	X	X	X	X	
EQ-5D-5L	X				X		X		X		
Sleep Disorders Inventory[f]	X				X		X		X		
Assessment of concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X

	Baseline[b]	Treatment Period									Follow-Up[k]
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**	**Week 56**
Type of visit	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Phone call
Allowable visit window (# days)		±3	±3	±3	±3	±7	±7	±7	±7		+4
Assessment of AEs[g]	X	X	X	X	X	X	X	X	X	X	X
Dispense study drug[h]	X[i,j]	X	X	X	X	X	X	X		X	
Study drug accountability	X[j]	X	X	X	X	X	X	X	X	X	

Table footnotes and abbreviations on next page

Abbreviations: AE(s)=adverse event(s); CGI-S=Clinical Global Impression-Severity; C-SSRS=Columbia-Suicide Severity Rating Scale**;** ECG=electrocardiogram; EOT/ET=end-of-treatment/early termination; EQ-5D-5L=5-level EuroQol-5D; ESRS-A=Extrapyramidal Symptom Rating Scale - Abbreviated; GCAS=Global Clinician Assessment of Suicidality; MMSE=Mini-Mental State Examination

[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 9), or a +4-day window (Visit 10) calculated from the Baseline Visit.

[b] Subject and study partner/caregiver 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 or early termination (ET) visit (if the study was ended early by the Sponsor). Data from the EOT/ET visit procedures of the antecedent study will be carried over as baseline information in the present study, as applicable.

[c] A single 12-lead ECG can be performed any time before blood sampling or at least 30 minutes after blood sampling during clinic visits.

[d] A urine pregnancy test may 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.

[e] The scale used in the antecedent study should also be used in the ACP-103-047 study. If the subject was previously assessed with the C-SSRS and is no longer able to reliably complete the C-SSRS in the Investigator's judgment, the GCAS should be administered and used thereafter in the present study.

[f] Appropriate consent/assent needs to be collected before assessment at Baseline.

[g] All ongoing AEs from the antecedent study will be carried over after informed consent has been obtained for the ACP-103-047 study and recorded from Baseline for the present study until resolution or the follow-up safety assessment. AEs occurring after the first dose of open-label study drug until 30 days after the last dose of open-label study drug in the antecedent study will be recorded as an AE in the ACP-103-047 study.

[h] Study drug will be dispensed to the subject at either scheduled or unscheduled visits.

[i] Study drug will be dispensed to the subject to take home at the Baseline visit. The subject and study partner/caregiver will be provided instructions to take the first dose of study drug on the following day.

[j] The used and unused treatment kits, blister cards, and tablets from the antecedent study are to be collected by the Investigator as part of the EOS/ET visit of the antecedent study before study drug for the present study can be dispensed.

[k] This visit is a safety follow-up telephone call visit for subjects who complete the study or who discontinue prematurely from the study. This visit will occur 30 (+4) days after the last dose of study drug.

3.3 Randomization

Not applicable.

3.4 Blinding

This is an open-label study.

3.5 Determination of Sample Size

Up to approximately 750 subjects will be enrolled. The sample size for this study is not based on statistical power, but will depend on the number of subjects who transition into this OL extension study from the antecedent study.

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 Data Management Plan [DMP] Appendix B). Recruitment efforts into the antecedent study (ACP-103-046), and roll-overs into the open-label extension study (ACP-103-047), were paused. The impact of COVID-19 on statistical analysis is discussed in each of the relevant sections of this SAP.

4 ANALYSIS SETS

4.1 Enrolled Subjects

Enrolled subjects are defined as those subjects who signed informed consent (from either the subject or legally accepted representative) for Study ACP-103-047, excluding rollover failures. Data listings will include all enrolled subjects.

4.2 Safety Analysis Set

The Safety Analysis Set will include all enrolled subjects who have taken at least 1 dose of OL study drug. The Safety Analysis Set will be used for all analyses.

5 DATA HANDLING CONVENTIONS

All data collected in this 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, medians, and confidence intervals 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.

All endpoints will be summarized using the Safety Analysis Set.

No hypothesis testing is planned. Descriptive summaries of all safety and efficacy endpoints will be provided.

5.2 Treatment Cohorts

Summaries by cohort based on the antecedent study treatment group will also be provided. The cohorts are defined as follows:

- Cohort 1: DB placebo – OL pimavanserin
- Cohort 2: DB pimavanserin – OL pimavanserin

The DB treatment group will be based on the treatment actually received in the antecedent study, in the event that it is different from the randomized treatment assignment.

For each continuous measure in safety and efficacy analyses, change from Baseline results will be presented in two ways:

- Using the Baseline from Study ACP-103-047 and reporting the changes across OL Study ACP-103-047 timepoints.
- Using the Baseline from the antecedent study and reporting changes (observed values) across the timepoints of both the antecedent study and the OL Study ACP-103-047.

5.3 Derived Variables

In general, all 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 total scores will be presented in data listings.

5.3.1 CGI-S

The CGI-S scale is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40 and Week 52/ET visits.

The CGI-S is a clinician-rated, 7-point scale that is designed to rate the severity of the subject's neuropsychiatric symptoms at the time of assessment using the Investigator's judgment and past experience with subjects who have the same condition. The 7-point scores are: 1=normal, not at all ill; 2=borderline ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6 =severely ill; 7=among the most extremely ill.

Missing CGI-S scores will not be imputed.

5.3.2 EQ-5D-5L Proxy Version 1

The EQ-5D-5L is assessed at Baseline, Week 12, Week 28, and Week 52/ET.

The EQ-5D-5L is a standardized instrument used as a measure of health outcome. The EQ-5D-5L Proxy version 1 will be used in this study. In this version, a caregiver (the proxy) is asked to rate the subject's health-related quality of life in their (the proxy's) opinion. The EQ-5D-5L consists of 2 components: the descriptive system, and the visual analogue scale (VAS).

The EQ-5D-5L descriptive system consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which has 5 potential responses. The responses record 5 levels of severity within a particular EQ-5D-5L dimension: 1=no problems; 2=slight problems; 3=moderate problems; 4=severe problems; 5=extreme problems. The responses for the 5 dimensions are combined into a single 5-digit code that describes the subject's health state.

The EQ-5D-5L VAS records the subject's health on a vertical visual analogue scale, where the upper endpoint is labeled "The best health you can imagine" and is numbered 100, while the lower endpoint is labeled "The worst health you can imagine" and is numbered 0. The EQ-5D-5L VAS will be treated as a continuous endpoint.

Missing values will not be imputed for either the EQ-5D-5L descriptive system or the VAS.

5.3.3 SDI

The SDI is assessed at Baseline, Week 12, Week 28, and Week 52/ET.

The SDI is an expanded version of one item of the Neuropsychiatric Inventory (NPI), consisting of the 7 subquestions from the NPI sleep disturbance item. Each of the subquestions was made into a separate question with frequency, severity, and caregiver distress rated by the caregiver with respect to the patient-participant for the 2 weeks prior to the visit. Thus, in contrast to a single rating for frequency and severity for all sleep

disturbance-related behaviors, which would be incorporated into an overall NPI score, the SDI score is derived after the caregiver rates the frequency and severity of each of the 7 separate sleep disturbance symptoms. Caregiver distress ratings are not part of the SDI total score, but distress is measured. The SDI total score is calculated as the average of seven frequency ratings × average of seven severity ratings, with a range of 0-12.

If the frequency rating and/or the severity rating is missing for a single item, then the total score will be imputed as the average of the non-missing frequency ratings × the average of the non-missing severity ratings. Otherwise, if more than one item has a missing frequency and/or severity rating, the total score will not be derived.

5.3.4 C-SSRS

The C-SSRS is assessed (when applicable) at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40 and Week 52/ET visits.

The Columbia-Suicide Severity Rating Scale (C-SSRS) will be used to assess suicidal ideations and behaviors in subjects who are able to complete the assessment (subjects without dementia, defined as an MMSE≥25), and subjects with dementia who the Investigator has determined can complete the C-SSRS. The C-SSRS monitors changes in suicidal thinking and behavior over time, in order to determine risk. Four constructs are measured: the severity of ideation, the intensity of ideation, behavior, and lethality.

The C-SSRS version assessing information since the last visit will be completed at all visits (including the Baseline visit). The C-SSRS results for each subject should be reviewed by the Investigator at each visit. If at any time the C-SSRS results for a given subject reveal potential suicidality, then the Investigator should assess the clinical significance of such results. If a clinically significant risk of suicidality is identified for a subject, then the Investigator should discontinue the subject and implement appropriate treatment.

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.

Missing C-SSRS item scores will not be imputed.

5.3.5 GCAS

The GCAS (when applicable) is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40 and Week 52/ET visits.

If the subject is not able, in the Investigator's judgement, to reliably complete the C-SSRS the Global Clinical Assessment of Suicidality (GCAS) will be administered and used thereafter in the study. If the GCAS was used in the antecedent study, suicidality since last visit will be assessed at Baseline and at all other visits. The first assessment with the GCAS should assess lifetime suicidality and suicidality for the past 3 months, and at all other visits suicidality since the previous visit will be assessed.

The GCAS is a clinician-rated, 5-point scale that is designed to rate the subject's suicidality based on the report of the subject, the report of the study partner/caregiver, and the clinician's global assessment. Ratings are scored as follows:0=absent; 1=feels life is not worth living; 2=wishes he/she were dead or any thoughts of possible death to self; 3=suicidal ideas or gesture; 4=attempt at suicide. The Investigator will record a subject rating, a study partner/caregiver rating, and a clinician rating.

Missing scores will not be imputed.

5.3.6 ESRS-A

The ESRS-A is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40 and Week 52/ET visits.

The ESRS was developed to assess 4 types of drug-induced movement disorders (Parkinsonism, akathisia, dystonia, and tardive dyskinesia) with established reliability, validity, and sensitivity. The ESRS-A, an accepted modified form of the original ESRS, will be used during the study to monitor for any worsening in extrapyramidal symptoms or signs at scheduled and unscheduled visits.

The ESRS-A consists of 4 subscales and 4 clinical global impression movement severity (CGI-S) scales of Parkinsonism, dyskinesia, dystonia, and akathisia. Each item of the subscales and each CGI-S rating is scored on a 6-point scale with higher scores denoting more severe drug-induced movement disorders: 0=absent; 1=minimal; 2=mild; 3=moderate; 4=severe; 5=extreme.

The 4 ESRS-A subscales are defined as follows.

- Parkinsonism subscale: 10 items (minimum=0, maximum=50)
    - P1 Rigidity: Upper limbs
    - P2 Rigidity: Lower limbs
    - P3 Rigidity: Neck

- P4 Tremor: Face, jaw/chin, lips, head
- P5 Tremor: Upper limbs/hands
- P6 Tremor: Lower limbs/feet
- P7 Reduced facial expression/speech
- P8 Impaired Gait/Posture
- P9 Postural Instability
- P10 Bradykinesia/Hypokinesia

- Dystonia subscale: 6 items (minimum=0, maximum=30)
  - DT1 Tongue
  - DT2 Jaw
  - DT3 Eyes, upper face, lower face, larynx
  - DT4 Shoulders, upper limbs, hands
  - DT5 Hips, lower limbs, feet
  - DT6 Trunk, neck
- Dyskinesia subscale: 6 items (minimum=0, maximum=30)
  - DK1 Tongue
  - DK2 Jaw
  - DK3 Eyes, upper face, lower face
  - DK4 Shoulders, upper limbs, hands
  - DK5 Hips, lower limbs, feet
  - DK 6 Trunk, neck
- Akathisia subscale: 2 items (minimum=0, maximum=10)
  - A1 Objective (observed during patient examination)
  - A2 Subjective

The ESRS-A total score is calculated as the sum of the 24 item scores with a possible range of 0 to 120. If 4 or fewer items are missing, then the total score for a given subject and timepoint will be imputed as the mean of the non-missing items multiplied by 24 and rounded to the nearest integer. If more than 4 items are missing, the total score will not be derived.

Missing ESRS-A item scores, subscale total scores, and CGI-S scores will not be imputed.

5.3.7 MMSE

The MMSE is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40 and Week 52/ET visits.

The MMSE is a 30-item questionnaire that includes simple questions and problems in the following areas: time and place of testing, repeating lists of words, arithmetic, language use

and comprehension, and copying or drawing. The MMSE is being used in this study to screen for cognitive impairment and as a safety measure.

Each of the 30 items has 2 possible values: 0=incorrect; 1=correct. The MMSE total score will be derived as the sum of the 30 item scores, thus the total score has a potential range of 0 to 30, with lower scores indicating more severe cognitive impairment.

If 6 or fewer items are missing, then the total score for a given subject and timepoint will be imputed as the mean of the non-missing items multiplied by 30 and rounded to the nearest integer. If more than 6 items are missing, the total score will not be imputed.

5.4 Analysis Visit Windows

In general, the OL Baseline assessment is defined as the last non-missing, including those from repeated and unscheduled measurements, within 30 days before the first OL dose date or on the first OL 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 2 below.

Table 2 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
Follow-up	395	380 to 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 date. Study day 1 is the first OL dose date.

5.4.1 Unscheduled Assessments

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

5.4.2 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-OL Baseline minimum, and overall post-OL Baseline maximum, all non-missing post-OL 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.

When replicate ECGs are collect at a given timepoint (typically, in triplicate), the average of the replicate values (i.e., PR interval, QRS duration, QT interval, QTcB interval, QTcF interval, and RR interval) will be considered as one assessment for the analyses.

5.5 Data Handling Conventions

5.5.1 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 date of the end-of-study/early termination visit will be used in the calculation of treatment duration. 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 any data summarization before final database lock, if a subject is still ongoing, then the last dose date will be imputed using the database extract date.

5.5.2 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 10 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.

5.5.3 Missing or Incomplete Dates for Adverse Events

Missing or incomplete AE start dates will be imputed for the purpose of determining whether the AEs are TE (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 TE. 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.

5.5.4 Missing Severity Assessment for Adverse Events

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

5.5.5 Missing Relationship to Study Drug for Adverse Events

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

5.5.6 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 ENROLLMENT AND DISPOSITION

The number of sites that enrolled at least 1 subject and the number of subjects enrolled will be summarized by region (North America, Europe, and rest of world) and overall. For enrolled subjects, the number and percentage of subjects in the Safety Analysis Set will be summarized by region (North America, Europe, or rest of world). 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 who completed or discontinued (all discontinued and by discontinuation reason) the study will also be summarized by region and overall for the Safety Analysis Set. Early terminations of subjects due to COVID-19 related reasons will be captured in the eCRFs and summarized.

7 PROTOCOL DEVIATIONS

Protocol deviations that occur during Study ACP-103-047 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 will be 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.

Similarly, three data listings of major protocol deviations will be provided: All deviations, COVID-19 related protocol deviations, and non COVID-19 related protocol deviations. Additionally, a data listing of all minor COVID-19 related protocol deviations will be provided.

A listing of protocol deviations will also be presented in three ways as described above.

8 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographics and OL Baseline characteristics will be summarized using descriptive statistics. Summaries by region (North America, Europe, or rest of world) will also be presented.

8.1 Demographics

Demographic variables include age, sex, primary race (subjects of multi-racial background can only identify/select one primary race on eCRF, or choose “other” and specify), ethnicity, height, weight, body mass index (BMI), region, subject living situation, and partner/caregiver relationship.

The reported age reflects a subject’s age at the OL Baseline visit date. Age and BMI will be presented as both continuous and categorical variables. Age categories will be presented as <65, 65 to 74, 75 to 84, and ≥85 years old. BMI categories (kg/m^2) will be presented as <25, 25 to 30, and >30.

8.2 Disease Characteristics and Neuropsychiatric History

Disease characteristics at OL Baseline will be summarized using descriptive statistics. MMSE total score, CGI-S, EQ-5D-5L VAS, SDI total score, and ESRS-A total score will be presented as continuous variables. In addition, CGI-S will be presented as a categorical

variable using categories of 1 to 7, and MMSE will be presented as a categorical variable using categories of≤10, 11 to 17, 28 to 24, and 25 to 30. For the C-SSRS the number and percentage of subjects having suicidal ideation or behavior since the last visit will be presented. For the GCAS, the number and percentage of subjects within each rating since the last visit (absent, feels life is not worth living, wishes he/she were dead or any thoughts of possible death to self, suicidal ideas or gestures, and attempts at suicide) will be presented.

Neuropsychiatric history will be summarized descriptively for continuous and categorical variables. The OL Baseline visit date will be used as the reference date for calculation of durations. For both the Disease Characteristics and Neuropsychiatric History, summaries by region (North America, Europe, and rest of world) will also be presented. The Neuropsychiatric history will be pushed into the -047 database from the -046 study. If there have been any changes in the subject's neuropsychiatric history since completing this form for the -046 study, appropriate updates should be made by editing the affected fields.

9 MEDICAL HISTORY

Medical and surgical history data will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or newer. The subject incidence will be summarized for each system organ class (SOC) and preferred term (PT). A subject will be counted only once per SOC or per PT for the summary.

A listing of the SOC, PT, 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 at OL Baseline will be provided.

10 CONCOMITANT AND POST-TREATMENT MEDICATION

Medications will be coded using WHO Drug Dictionary (WHODRUG-DDE-B2) 2019 March or newer version. For concomitant medications, the number and percentage of subjects taking each drug class (ATC Level 3) and medication PT will be tabulated. A subject will be counted only once per drug class or per medication PT for the summary. Concomitant and post-treatment medications will be summarized separately.

10.1 Concomitant Medication

Concomitant medication is defined as any medication with a start date prior to the date of the OL first dose date and continuing after the OL first dose date, or with a start date between the OL first dose date and OL last dose date, inclusive.

10.2 Post-Treatment Medication

Post-treatment medication is defined as any medication with a start date after the OL last dose date.

10.3 COVID-19 Related Medications

Relationship to COVID-19 will be assessed by the investigator as detailed in the DMP Appendix B. Concomitant and post-treatment medication analyses described in Section 10.1 and Section 10.2 above will also be summarized by relationship to COVID-19 (Not related to COVID-19 vs. Related to COVID-19).

11 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

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

11.1 Exposure to Study drug

Pimavanserin dose levels are expressed as free base.

For each subject the duration of exposure will be calculated as the number of days from first dose date to last dose date inclusive. See Sections 11.1.1 and 11.1.2 for further details.

11.1.1 Exposure to OL pimavanserin

Formulas to calculate subject level exposure-related quantities for OL pimavanserin are given as follows:

$$Duration\ of\ OL\ exposure\ (days) = OL\ last\ dose\ date - OL\ first\ dose\ date + 1$$

$$Average\ OL\ daily\ dose\ (mg/day) = \frac{cumulative\ OL\ dose\ (mg)}{duration\ of\ OL\ pimavanserin\ exposure\ (days)}$$

The total cumulative dose of pimavanserin will be calculated by first multiplying the number of tablets taken by the dose level (in mg) for each kit returned to the site during the OL study period and then summing the results for all kits.

If a subject has an unreturned kit then the overall cumulative dose and average daily dose will be set to missing

Duration of OL pimavanserin exposure will be summarized as both continuous and categorical variables. For the categorical presentation of duration of OL exposure the number and percentage of subjects in each of the following categories will be displayed: <2 weeks

(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), 16 to <28 weeks (112 to 195), 28 to <40 weeks (196 to 279), 40 to <52 weeks (280 to 363), and ≥52 weeks (≥364 days).

In addition, whether a subject had any dose changes (yes vs. no), and last dose level (20 mg vs. 34 mg) will be tabulated.

Kaplan-Meier curves of duration of exposure to OL pimavanserin will be provided.

11.1.2 Total exposure to double-blind and OL pimavanserin

For subjects who received pimavanserin in the antecedent study, formulas to calculate subject level total pimavanserin (DB+OL) exposure-related quantities are as follows:

$$\textit{Total duration of exposure (days)} = \textit{(OL last dose date} - \textit{OL first dose date} + 1) + \textit{(DB last dose date} - \textit{DB first dose date} + 1)$$

$$\textit{Total average daily dose(mg/day)} = \frac{total\ cumulative\ dose\ (mg)}{total\ duration\ of\ exposure\ (days)}$$

In case a subject whose last dose date in the antecedent study is equal to the first dose date in the OLE, the total duration of exposure will be the above calculation minus one.

The total cumulative dose of pimavanserin will be calculated by first multiplying the number of tablets taken by the dose level (in mg) for each kit returned to the site during both the DB and OL study periods and then summing the results for all kits.

For subjects who received placebo in the antecedent study, the pimavanserin total duration of exposure, total cumulative dose, and the average daily dose across the DB and OL periods will use the same values as calculated for the OL study alone (see Section 11.1.1).

Total duration of DB+OL exposure to pimavanserin will be summarized as both continuous and categorical variables. For the categorical presentation, the number and percentage of subjects in each of the following categories will be displayed: <2 weeks (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 <24 weeks (112 to 195 days), 28 to <40 weeks (196 to 279 days), 40 to <52 weeks (280 to 363 days), 52 to <60 (364 to 419 days), and ≥60 weeks (≥420 days).

In addition, summaries of whether subjects had any dose change (yes vs. no), their highest dose level (20 mg or 34 mg), and their last dose level (20 mg or 34 mg) will also be provided.

11.2 Measurement of Study Drug Compliance

Study drug compliance (in percentage) during the OL study period for a given subject is calculated as follows:

$$Compliance = \left[\frac{OL\ \ tablets\ dispensed - OL\ tablets\ returned}{2 \times duration\ of\ \ OL\ exposure}\right] \times 100\%$$

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

12 EFFICACY ANALYSES

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

12.1 Exploratory Efficacy Endpoints

The exploratory endpoints for this study to assess the benefit of pimavanserin are:

- Change from Baseline in CGI-S scale for neuropsychiatric symptoms
- Change from Baseline in SDI score
- Change from Baseline in EQ-5D-5L 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 5.3 will not be imputed.

12.4 Multiple Comparisons / Multiplicity

No hypothesis testing is planned.

13 METHODS OF EFFICACY ANALYSES

13.1 Analysis of Efficacy Endpoints

Descriptive statistics for all exploratory efficacy endpoints listed in Section 12.1 will be tabulated by cohorts based on antecedent study and DB treatment group at scheduled timepoints. The summaries of the change from Baseline results will be presented by cohort at

scheduled timepoints in two ways as specified in Section 5.2. The scheduled timepoints across the DB and OL study periods for all efficacy endpoints are presented in Table 3 below.

Table 3 Scheduled Assessment Timepoints for Efficacy Endpoints Across ACP-103-046 (DB) and ACP-103-047 (OL)

	CGI-S	SDI	EQ-5D-5L
DB Baseline	x	x	x
DB Week 1	x		
DB Week 2	x		
DB Week 4	x	x	
DB Week 6	x		
DB Week 8/OL Baseline (-046 EOT)	x	x	x
OL Week 2	x		
OL Week 4	x		
OL Week 8	x		
OL Week 12	x	x	x
OL Week 16	x		
OL Week 28	x	x	x
OL Week 40	x		
OL Week 52	x	x	x

13.1.1 EQ-5D-5L

The change from Baseline in the EQ-5D-5L VAS score will be summarized descriptively at each timepoint as described in Section 13.1.

For each EQ-5D-5L dimension the proportion of subjects reporting no, slight, moderate, severe, and extreme/unable to perform activity will be summarized descriptively at each timepoint.

Change from OL Baseline in EQ-5D-5L health state will be assessed with the Pareto classification of health change (PCHC) method. Using this methodology, at each scheduled

timepoint, each EQ-5D health state will be classified into one of four categories, relative to the OL Baseline health state:

- Improved = improved on at least one dimension and not worsened on any other dimension
- Mixed = improved on at least one dimension and worsened on at least one other dimension
- No change = no changes in any dimension
- Worsened = deterioration on at least one dimension and no improvement on any other dimension

If one or more dimensions are missing a valid response, then the PCHC category will not be derived.

The proportion of subjects in each PCHC category will be summarized descriptively at each scheduled timepoint.

The above analyses will also be presented based on the DB cohorts as described in Section 5.2.

14 SAFETY ANALYSES

Safety variables include AEs, TEAEs, clinical laboratory variables, vital signs, body weight, BMI, physical examinations, electrocardiogram (ECG), C-SSRS, GCAS, MMSE, and ESRS-A variables. The safety summaries will be presented for the Safety Analysis Set using descriptive statistics. Safety variables will be summarized by cohorts based on the antecedent study and DB treatment group (see Section 5.2). For each continuous variable in clinical laboratory, vital signs, and electrocardiograms, the change from Baseline will be presented in two ways as specified in Section 5.2.

The scheduled timepoints across the DB and OL study periods for all safety endpoints are presented in Table 4 below.

Table 4 Scheduled Assessment Timepoints for Safety Endpoints Across ACP-103-046 (DB) and ACP-103-047 (OL)

	Vitals	Lab	ECG	MMSE	ESRS-A
DB Baseline	x	x	x	x	x
DB Week 1	x			x	x
DB Week 2	x		x	x	x
DB Week 4	x	x		x	x
DB Week 6	x			x	x
DB Week 8/OL Baseline (-046 EOT)	x	x	x	x	x
OL Week 2	x		x	x	x
OL Week 4	x		x	x	x
OL Week 8	x		x	x	x
OL Week 12	x	x	x	x	x
OL Week 16	x		x	x	x
OL Week 28	x		x	x	x
OL Week 40	x		x	x	x
OL Week 52	x	x	x	x	x

For by-visit summaries, all scheduled and unscheduled values within a visit window will be considered. For the overall post-Baseline summaries, all post-Baseline values will be considered, including unscheduled and out of window values.

14.1 Adverse Events

All AEs, classified by preferred term, will be coded using MedDRA version 23.0 or newer.

An AE (classified by PT) will be considered a TEAE if it started on or after the OL first dose of study drug and no later than the OL last dose date + 30. AEs reported on Day 1 based on pre-dose findings will not be considered as TEAEs.

For the following summaries, the event counts and the number and percentage of subjects reporting TEAEs will be tabulated by cohort and overall:

- TEAEs by SOC and PT
- Most frequently reported TEAEs by SOC and PT
  - PTs reported by ≥5% and ≥2% (overall) of subjects in the Safety Analysis Set
- TEAEs by PT
- TEAEs by SOC, PT, and maximum severity
  - if more than 1 AE occurs with the same PT for the same subject, the subject will be counted only once for that PT using the most severe occurrence
- TEAEs related to study drug by SOC and PT
- Treatment-emergent serious adverse events (TESAEs) by SOC and PT
- TEAEs leading to discontinuation of study drug by SOC and PT
- AEs with fatal outcome by SOC and PT
- TEAEs with fatal outcome (that occurred within 30 days of last dose) by SOC and PT

For tabulations that include SOC and PT the display will be sorted alphabetically by SOC and then by descending subject frequency for the PTs based on counts in the Safety Analysis Set within each SOC. SOCs will not be included in the TEAEs by PT tabulation. This display 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 TE, and will include the verbatim term in addition to the MedDRA SOC and PT. This listing will also include all relevant eCRF data associated with the event: e.g. date of onset, dose level at date of onset, date resolved, date of the first and last dose of study drug, 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). In these listings, an indicator for TEAEs will also be included.

14.1.1 Assessment of the Impact of COVID-19 on Adverse Events

The relationship of selected AEs to COVID-19 will be assessed by investigator as detailed in the DMP Appendix B. Each of the primary safety analyses described in Section 14.1 will be additionally summarized by relationship to COVID-19 (Not related to COVID-19 vs. Related to COVID-19).

14.2 Clinical Laboratory Variables

Clinical laboratory tests are performed at Baseline, Week 12, and Week 52/ET visits. 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 data listings, as well as a separate local laboratory PCI listing. 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.

14.2.1 Chemistry

Clinical chemistry serum tests include the following:

- Sodium (Na), potassium (K), chloride (Cl), phosphorus (P), calcium (Ca),), blood urea nitrogen (BUN), creatinine (CR), uric acid, , bicarbonate
- Alaninine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), total bilirubin (TBIL), lactate dehydrogenase (LDH)
- Glucose
- Albumin (ALB), total protein
- Creatine kinase (CK)/creatine phosphokinase (CPK)

14.2.2 Miscellaneous

- Prolactin
- Lipid panel
    - total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, very low density lipoprotein cholesterol

14.2.3 Hematology

Hematology tests include the following:

- Complete blood count (CBC) including:
    - White blood cell (WBC) count, absolute neutrophil count, complete differential (relative and absolute), hematocrit (Hct), hemoglobin (Hgb), red blood cells (RBC), platelets, reticulocyte count

14.2.4 Urinalysis

Urinalysis tests include the following:

- Blood, RBCs, WBCs, protein, glucose, ketones, specific gravity, pH, leukocyte esterase
- A urine pregnancy test should be performed at all designated visits for women of childbearing potential
  - If urine cannot be obtained in women of childbearing potential, a serum pregnancy test should be done in its place
- Urine drug screen will be performed at Baseline, Week 12, and Week 52

14.2.5 Methods of Analysis for Clinical Laboratory Variables

14.2.5.1 Observed Values and Change from Baseline

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 and maximum post-Baseline observed and change from Baseline values will also be summarized (for OL study period only).

For hemoglobin, hematocrit and uric acid, by-visit as well as post-OL Baseline minimum and maximum 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 each scheduled post-Baseline visit. For the categorical urinalysis by-visit summary, the denominator is the number of subjects with non-missing values for the given parameter, visit, and cohort.

Summaries of the above will also be presented for OL timepoints only using OL Baseline, and DB+OL timepoints using the DB Baseline from the antecedent study (see Section 5.2 and Table 4).

14.2.5.2 Shift Tables

Laboratory values will 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 each scheduled post-Baseline visit relative to the same classification at the Baseline visit. Shift tables will be presented for shift from OL Baseline as well as shift from DB Baseline. 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 and cohort.

The shifts from Baseline to overall post-Baseline minimum and overall post-Baseline maximum will also be presented. The denominator is the number of subjects with non-missing Baseline and at least 1 post-Baseline value for the given parameter and cohort.

For hemoglobin, hematocrit and uric acid, by-visit as well as post-Baseline minimum and maximum will be presented for each gender as well as for both genders combined.

Shift tables will be presented for OL timepoints only using OL Baseline, and DB+OL timepoints using the DB Baseline from the antecedent study (see Table 4).

14.2.5.3 Potentially Clinically Important Laboratory Values

The 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 5 and Table 6. Subjects with multiple PCI values for a given parameter will be counted only once for that parameter. All post-Baseline values will be considered, including unscheduled and out of window values. PCI tables will be presented for OL timepoints only using OL Baseline, and DB+OL timepoints using the DB Baseline from the antecedent study (see Section 5.2 and Table 4).

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, visit, and cohort, and the denominator is the number of subjects with non-missing values for the given parameter, visit, and cohort. 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 cohort, and the denominator is the number of subjects with at least 1 post-Baseline value for the given parameter and cohort. 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-103-047 will be provided. This listing will include all observations from study ACP-103-047 for those subjects and parameters for which at least one PCI value (including OL Baseline) was observed.

Table 5 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 6 Criteria for Potentially Clinically Important Laboratory Values - Urinalysis

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

14.2.5.4 Data Listings

All laboratory test results will be listed. The listings will include date and study day of collection. Out of range values will be flagged in the data listings (e.g., as 'L' or 'H'). Central and local laboratory values will be presented separately.

A listing of all PCI values will be provided. This listing will include all observations for those subjects and parameters for which at least one PCI value (including Baseline) was observed. Central and local laboratory PCI listings will be presented separately.

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

14.3 Vital Signs

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

Due to COVID-19 disruptions it may be necessary for vital signs to be collected outside of the clinic by persons other than study site staff. These results will not be included in any summary data analysis; they will, however, be presented in data listings, and in a separate PCI listing of vitals measured by persons other than study site staff.

14.3.1 Vital Signs Variables

Vital signs include weight, height (measured at Screening of antecedent study), derived BMI, sitting systolic blood pressure (SBP), sitting diastolic blood pressure (DBP), pulse rate, temperature, and respiratory rate. The sitting blood pressure should be measured after the subject has been sitting for ≥3 minutes.

14.3.2 Vital Signs Methods of Analysis

Vital signs 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 7. 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, visit and cohort, and the denominator is the number of subjects with non-missing values for the given parameter, visit and cohort. 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 cohort, and the denominator is the number of subjects with at least 1 post-Baseline value for the given parameter and cohort.

Vitals change from Baseline and PCI tables will be presented for OL timepoints only using OL Baseline, and DB+OL timepoints using the DB Baseline from the antecedent study (see Section 5.2 and Table 4).

A listing of all PCI values will be provided (excluding those vitals collected by persons other than study site staff). There will be a separate PCI listing for vitals collected by persons other than study site staff. These listings will include all observations for those subjects and parameters for which at least one PCI value (including Baseline) was observed

Table 7 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)

ECG is performed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and Week 52/ET.

All tracings will be evaluated by a central reading laboratory, including any collected outside of the clinic due to COVID-19 disruptions when possible.. At the Baseline visit the

machine-read results will also be recorded. ECG data summaries, including the cardiologist's interpretation, will be analyzed using the centrally evaluated data.

14.4.1 ECG Variables

ECG variables include heart rate, PR interval, RR interval, QRS interval, QT interval, and QTc intervals. QTc intervals include QTcB (Bazett's formula) and QTcF (Fridericia's formula). QTcF will also be categorized into the following categories (msec):

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

14.4.2 ECG Methods of Analysis

14.4.2.1 Observed Values and Change from Baseline

Observed values and the changes from Baseline of ECG variables will be summarized using descriptive statistics at Baseline and all scheduled post-Baseline visits. For the QTcF categorical analysis, the number and percentage of subject in each category will be summarized at each scheduled visit as well as overall post-Baseline maximum (only for the OL study period).

14.4.2.2 PCI Values

Electrocardiogram values will be considered PCI if they meet or exceed the upper limit values listed in Table 8. The number and percentage of subjects with PCI values will be summarized at scheduled post-Baseline visits and for overall post-Baseline (only for the OL study period). 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, visit and cohort, and the denominator is the number of subjects with non-missing values for the given parameter, visit and cohort. 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 cohort, and the denominator is the number of subjects with at least 1 post-Baseline value for the given parameter and cohort.

Table 8 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

14.4.2.3 Cardiologist Interpretations

For cardiologist's interpretations, the number and percentage of subjects with ECG results that are classified as normal or abnormal will be summarized at scheduled visits. The overall post-baseline worst interpretation (i.e. if a subject has one or more ECG results that are considered as abnormal, this subject will be counted in the abnormal category) will also be summarized (only for the OL study period). 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 (only for the OL study period) 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 given cohort. 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 for the given cohort.

14.4.2.4 Data Listings

All data, including machine-read Baseline results, will be listed. A listing of all ECG PCI values in study ACP-103-047 will be provided. This listing will include all observations from study ACP-103-047 for those subjects and parameters for which at least one PCI value (including Baseline) was observed.

14.5 Physical Examination

Physical examination is performed at Baseline, Week 28, and Week 52/ET visits.

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

14.6 Other Safety Variables

14.6.1 ESRS-A

The ESRS-A is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40, and Week 52/ET visits.

The ESRS-A total score and the 4 individual global CGI-S scores will be summarized using descriptive statistics at Baseline and scheduled post-Baseline visits. The change from Baseline scores will also be summarized at scheduled post-Baseline visits. For each of the above endpoints, results will be presented for OL timepoints only using OL Baseline, and DB+OL timepoints using the DB Baseline from the antecedent study (see Section 5.2 and Table 4).

The individual item scores and subscale scores will be listed but not summarized.

14.6.2 MMSE

The MMSE is assessed at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40 and Week 52/ET visits.

The MMSE total score will be summarized using descriptive statistics at Baseline and scheduled post-Baseline visits. The change from Baseline scores will also be summarized at scheduled post-Baseline visits. The MMSE total score will be presented for OL timepoints only using OL Baseline, and DB+OL timepoints using the DB Baseline from the antecedent study (see Section 5.2 and Table 4).

The individual item scores will be listed but not summarized.

14.6.3 Suicidality

The C-SSRS will be administered if the subject, in the Investigator's judgement, is able to reliably complete it. Otherwise, the GCAS will be administered and used thereafter in the study.

14.6.3.1 C-SSRS

The C-SSRS is assessed (when applicable) at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40 and Week 52/ET visits.

The event counts and the number and percentage of subjects reporting any post-OL Baseline 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), suicidal behavior (preparatory acts or behavior; aborted attempt; interrupted attempt; actual attempt; suicide), or suicidality (any suicidal ideation or behavior) will be tabulated.

The event counts and the number and percentage of subjects reporting any post-OL Baseline non-suicidal self-injurious behavior will also be tabulated.

For calculating the percentages, the denominator will be the number of subjects with an OL C-SSRS assessment within each cohort. The above summaries will be presented only for the OL study period.

14.6.3.2 GCAS

The GCAS is assessed (when applicable) at Baseline, Weeks 2, 4, 8, 12, 16, 28, 40 and Week 52/ET visits.

The overall post-OL Baseline worst suicidality rating will be summarized using the number and percentage of subjects within each rating. The number and percentage of subjects

reporting any post-OL Baseline rating of 3 or 4 will be tabulated. For calculating percentages, the denominator is the number of subjects with an OL GCAS assessment at the given visit and within each cohort. The above summaries will be presented only for the OL study period and using the clinician ratings.

Subject and study partner/caregiver ratings will not be summarized but will be included in data listings.

15 CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

16 INTERIM ANALYSIS

One or more interim analyses may be conducted in order to support safety and efficacy evaluations for regulatory submissions.

16.1 Interim Analyses

The ACP-103-046 database lock for the first interim analysis (IA-1) occurred on December 13, 2019 (under version 1 of the SAP), and included data from 288 subjects whose last visit occurred on or before December 2, 2019. Of these subjects, 231 rolled-over into ACP-103-047 and were included in IA-1. A second interim analysis occurred on July 2, 2020 (for purposes of a 120 day update) and included 504 subjects. Of these, 353 rolled over into ACP-103-047 and are to be included in IA-2. The rate of rollovers was lower for IA-2 because of the temporary suspension of enrollment into ACP-103-047, beginning on March 20, 2020, due to COVID-19 disruptions.

17 DATA MONITORING/REVIEW COMMITTEE

Safety data are monitored throughout the study and aggregate safety reports are produced and reviewed approximately quarterly. Furthermore, selected safety data from this study will be presented periodically to the Data and Safety Monitoring Board (DSMB) along with data from the ACP-103-046 study to assist with interpretation of benefit versus risk in that study.

18 COMPUTER METHODS

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® software (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 Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, March 2020.

21 APPENDICES

21.1 Summary of Version Changes

Version No:	Document History Description of Update	Author(s)	Version Date
1.0	Original version	[redacted]	26 NOV 2019
2.0	Updated to include handling of analyses related to COVID-19	[redacted]	15 JUL 2020
3.0	In alignment with Protocol Amendment 4 changes were made to indicate that exploratory efficacy data from interim analyses conducted in this study may also be evaluated in order to support regulatory submissions.	[redacted]	08 March 2021