**Official Title**: A multi-center, open-label extension study to examine the safety and tolerability of ACP-103 in the treatment of psychosis in Parkinson's Disease

**NCT Number**: NCT00550238


**STATISTICAL ANALYSIS PLAN**

**Protocol Number: ACP-103-015**

# A Multi-Center, Open-Label Extension Study to Examine the Safety and Tolerability of ACP-103 in the Treatment of Psychosis in Parkinson's Disease

**ACADIA Pharmaceuticals Inc.**

[redacted]

**Version 1: 18 December 2013**

**Version 2: 05 August 2014**

**CONFIDENTIAL**

ACADIA
Pharmaceuticals

# Statistical Analysis Plan Approval Form

| | |
|---|---|
| **Protocol Number:** | **ACP-103-015** |
| **Study Title:** | A Multi-Center, Open-Label Extension Study to Examine the Safety and Tolerability of ACP-103 in the Treatment of Psychosis in Parkinson's Disease |
| **Version Date of Amendment 1:** | 05 August, 2014 |

**I have read and approve the statistical analysis plan for the study listed above.**

**Director, Biostatistics & SAS Programming**

[redacted]

06 AUG 2014
Date

**VP, Regulatory Affairs & Development**

[redacted]

10 November 2014
Date

**EVP, Development & CMO**

[redacted]

8 Aug 2014
Date

## TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACADIA | ACADIA Pharmaceuticals Inc. |
| AE(s) | Adverse Event(s) |
| ATC | Anatomical/Therapeutic/Chemical |
| BMI | Body mass index |
| BP | Blood pressure |
| CFB | Change from Baseline |
| CGI-I | Clinical Global Impression – Improvement |
| CGI-S | Clinical Global Impression - Severity |
| DBP | Diastolic blood pressure |
| EC | Ethics Committee |
| ECG(s) | Electrocardiogram(s) |
| eCRF | Electronic case report form |
| HIPAA | Health Insurance Portability and Accountability Act |
| HR | Heart Rate |
| ICF | Informed Consent Form |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mmHg | millimeters of mercury |
| msec | millisecond(s) |
| NDA | New drug application |
| NMSS | Non-Motor Symptoms Scale |
| PD | Parkinson’s Disease |
| PDP | Parkinson’s Disease psychosis |
| PE(s) | Physical Examination(s) |
| PK | Pharmacokinetic |
| PR | PR interval on an electrocardiogram tracing |
| QRS | QRS interval of electrocardiogram |
| QT | QT interval of electrocardiogram |
| QTc | QT interval of electrocardiogram; corrected for heart rate |
| QTcF | Corrected QT interval by the method of Fridericia |
| QTcB | Corrected QT interval by the method of Bazett |

| | |
|---|---|
| RUD-Lite | Resource Utilization in Dementia Lite |
| SAE(s) | Serious Adverse Event(s) |
| SAPS | Scale for the Assessment of Positive Symptoms |
| SAP-H+D | Combined SAPS-Hallucinations and Delusions Score |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SEM | Standard Error of the Mean |
| SOC | System Organ Class |
| SOP | Standard Operating Procedures |
| TEAE | Treatment-Emergent Adverse Event |
| UPDRS | Unified Parkinson's Disease Rating Scale |
| US | United States |
| WHO | World Health Organization |

## DEFINITIONS

The following definitions are developed for the purpose of statistical analysis and data tabulation.

| | |
|---|---|
| Adverse Event | An adverse event (AE) is any untoward medical occurrence or unintended change from the subject's pre-treatment condition, including inter-current illness, that occurs during the course of a clinical trial after treatment has started, whether considered related to study treatment or not. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. |
| Baseline | Baseline is defined as the last available measurement taken prior to the first study drug administration in the ACP-103-015 study. If an ACP-103-015 baseline assessment was not scheduled to be performed, then the baseline value will be taken from the last available measurement in the core study. |
| Change from Baseline | For any given parameter at any given visit, the change from baseline (CFB) is defined as the parameter value for the given visit minus the Baseline value. |
| Descriptive Statistics | Number of subjects, mean, median, standard deviation, standard error of the mean, minimum and maximum for continuous measurements; number and percentage of subjects in each level of a categorical measurement. |
| Safety Analysis Set | The safety analysis set includes all enrolled subjects who receive any study drug in the ACP-103-015 study. |
| Safety Assessments | • Adverse events<br>• Vital Signs<br>• Clinical Laboratory Tests<br>• Electrocardiogram (ECG)<br>• Physical Examinations |
| Baseline Procedures | Subjects enrolled within 1-week of completing the double-blind period a previous trial with pimavanserin are not required to undergo baseline procedures (except an update to the medical history and baseline RUD-Lite, Appendix A). If they were enrolled after 1-week, all baseline procedures were required. |

| | |
|---|---|
| Serious Adverse Event | A serious adverse event (SAE) is any AE with any of the following outcomes:<br>• Results in death;<br>• Is life-threatening (i.e., the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);<br>• Requires inpatient hospitalization or prolongation of existing hospitalization;<br>• Results in persistent or significant disability/incapacity;<br>• Is a congenital anomaly or birth defect;<br>• Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but based on appropriate medical judgment may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. |
| Scheduled Visit | A scheduled visit is any planned visit per the protocol schedule of events. |
| Study Day 1 | Study day 1 is defined as the date of first administration of study drug (pimavanserin) in the ACP-103-015 study. |
| Study Day *n* | Study day *n* represents a visit or assessment that occurs *n* days relative to the start of study drug in the ACP-103-015 study, computed as: (date of visit – study day 1) + 1 if the date of visit occurs on or after date of first dose; otherwise computed as: (date of visit – study day 1). Note that there is no day 0. |
| Study Duration | The duration of the open-label use of pimavanserin will be determined based on clinical evaluations but may continue for as long as this drug is considered to be well tolerated and efficacious, and until such time as pimavanserin is approved and commercially available |

| | |
|---|---|
| Treatment-Emergent Adverse Event | A treatment-emergent adverse event (TEAE) is defined as an adverse event started between first study dose date and 30 days after the last dose date in the ACP-103-015 study. |
| Treatment Group | All subjects will receive 40 mg of pimavanserin once per day (QD). |

# 0 REVISION HISTORY

This statistical analysis plan is amended to reflect the following changes:

- Added imputation rules for missing or partial medication end dates. See Section 5.4.3 for details.
- Added summary of disposition by Sponsor re-classified withdrawal reasons. See Section 5.5 for details.
- Concomitant medications are summarized by indication (motor function, dementia, psychosis, or other). See Section 5.9.2 for details.
- Removed redundant categorical analysis of caregiver burden scale (CBS) data. See Section 5.11.2 for CBS analysis.
- The criteria for markedly abnormal laboratory values was revised to reflect SI unit. See Appendix B for details.
- Various administrative text revisions to assure clarity.

# 1 INTRODUCTION

This statistical analysis plan covers the detailed procedures for performing statistical analyses and producing tables and listings in the study described in ACADIA Pharmaceuticals Inc. Protocol ACP-103-015 (Amendment 6, dated 30June2010).

# 2 STUDY OVERVIEW

## 2.1 General Study Design and Plan

This study will be conducted as a multi-center, open-label extension study. Subjects who have completed blinded treatment in a previous study of pimavanserin in Parkinson's Disease Psychosis (PDP), and who may, in the opinion of the Investigator, benefit from treatment with pimavanserin, will be enrolled in this extension study for safety evaluation. All subjects were required to have a caregiver. Subjects may be enrolled in ACP-103-015 as early as the last visit of the treatment phase of the prior blinded study OR up to 28 days following completion of this blinded treatment period.

Subjects who enroll in ACP-103-015 within one week of completion of the treatment phase of the prior blinded study will not be required to complete a full baseline visit (Day 1) (see Appendix A).

Subjects who are enrolled greater than one week following completion of the prior blinded study will be required to complete a full baseline evaluation for ACP-103-015.

Once per day, subjects will be administered 40 mg of pimavanserin (two 20 mg tablets), orally, preferably in the morning. Dose changes (increases or decreases) will NOT be allowed.

All subjects will be required to visit the study site at Week 2, Month 1, Month 3, Month 6, Month 9, Month 12, and every six months thereafter (every 3 months before Protocol

Amendment 6) to complete safety and clinical evaluations. Unscheduled clinical evaluations may occur at any time if deemed appropriate by the Investigator.

## 2.2 Study Procedures (Based on Protocol Amendment 6)

Before any subjects may be enrolled in the study, ACADIA and/or designee must obtain a copy of essential documents including the following:

- Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol;
- IRB- or EC-approved Informed Consent Form (ICF);
- Health Insurance Portability and Accountability Act (HIPAA) form (where appropriate);
- Other documents required by local regulations, as applicable.

Each subject must sign the approved ICF and, where appropriate, HIPAA forms prior to the administration of any measures required for this clinical study. Each subject's caregiver signed and dated an ICF. Each subject who meets all eligibility criteria will be assigned a unique identification number. No subject will be enrolled more than once in the study. Once the identification number has been assigned to a subject, no attempt should be made to use that number again.

The baseline day (Day 1) will represent the first day of the study and the first day of dosing with study drug in the ACP-103-015 study. Baseline evaluations will be conducted on Day 1, prior to administration of the first dose of study drug on that day. All subjects will be dosed with 40 mg of pimavanserin administered orally, once per day.

All subjects will be required to visit the study site at Week 2 (Day 14 ± 3 days), Month 1 (Day 28 ± 3 days), Month 3 (Day 84 ± 7 days), Month 6 (Day 168 ± 7 days), Month 9 (Day 252 ± 7 days), Month 12 (Day 336 ± 7 days), and every six months (every 168 days ± 7 days) thereafter to complete safety and clinical evaluations. (Note: Prior to Amendment No. 6, 30 June 2010, subjects had study visits beyond Month 12 performed every 3 months). Unscheduled clinical evaluations may occur at any time if deemed appropriate by the Investigator. If the subject terminates the study at any time other than a planned visit the subject will be required to visit the clinic for an end-of-study evaluation.

Blood samples for determination of pimavanserin plasma concentration will be obtained prior to study drug administration at Week 2, Month 1, Month 2, Month 3, Month 6, Month 9, Month 12, and every 6 months thereafter, and at end-of-study, .

Safety assessments (clinical safety laboratory tests, vital sign measurements, physical examinations, and electrocardiograms [ECGs]) will be conducted at scheduled times throughout the study. Adverse events (AEs) and the use of concomitant medications will be monitored from the time of informed consent through the final visit.

Appendix A displays the schedule of events and assessments.

### 2.3 Randomization and Blinding

Not applicable.

### 2.4 Sample Size Estimation

Not applicable.

## 3 STUDY OBJECTIVE AND ASSESSMENTS

### 3.1 Study Objective

The objective of this study is to assess the long-term safety and tolerability of pimavanserin for the treatment of PDP.

### 3.2 Clinical Rating Scales

The Caregiver Burden Scale, Clinical Global Impression-Severity (CGI-S), Clinical Global Impression–Improvement (CGI-I), and Unified Parkinson's Disease Rating Scale (UPDRS; a safety measure) parts II and III will be administered at all scheduled post-baseline visits. The Scale for the Assessment of Positive Symptoms (SAPS) will be administered at Month 1 only.

The Non-Motor Symptom scale (NMSS; a safety measure) for PD was initially collected in this study but was discontinued with amendment 6. Results will be presented in a data listing but will not be summarized.

The Resource Utilization in Dementia (RUD)-Lite (health economics outcome measure) will be collected at baseline (all subjects had a baseline RUD-Lite performed), Month 12, every 6 months thereafter, and at end of study.

### 3.3 Safety and Pharmacokinetic Endpoints

The safety and pharmacokinetic assessments include the following:

- AEs;
- Physical examinations (PEs);
- Vital signs and body weight;
- ECGs;
- Clinical Laboratory including clinical chemistry, hematology, and urinalysis;
- Pimavanserin plasma concentrations (trough).

## 4 ANALYSIS SETS

All analyses will be performed on the safety analysis set, which is defined as: all enrolled subjects who receive at least one dose of study drug (pimavanserin).

# 5 STATISTICAL CONSIDERATIONS

## 5.1 General Statistical Procedures

Statistical summaries will be generated using SAS® software, version 9.3 or higher. No formal statistical tests will be conducted. Unless otherwise specified, continuous parameters will be summarized using the following descriptive statistics: number of observations, mean, median, standard deviation (SD), standard error of the mean (SEM), minimum and maximum. Categorical parameters will be summarized using the number and percentage of subjects in each level of a category.

Descriptive statistics will be presented using a significant figure rule: the minimum and maximum will have the same number of significant figures as the data; the mean and median will have one more significant figure than the data being summarized; the SD and SEM will have two more significant figures than the data being summarized; and the sample size (n) will be reported as an integer.

Unless otherwise indicated, descriptive statistics will be reported for observed cases only and missing data will not be imputed. Missing observations will not be taken into account when calculating frequencies, unless otherwise indicated. By-visit summary tables will include all available subjects' data up to 4 years (192 weeks) on study, and any data beyond that point will be summarized in a single visit (>192 weeks). For laboratory, vitals, and ECGs by time period summaries an additional last assessment will be included.

Data listings will include all data for all subjects. Listings will present data sorted by site number, subject identification, study day, and visit (both nominal and derived, if applicable), unless otherwise specified. If a listing includes a derived visit, then in those cases where a subject has more than one result in the derived visit window the result that is used for analysis will be flagged in the listing.

## 5.2 Multiplicity Issues

Multiplicity is not an issue because there are no formal statistical analyses.

## 5.3 Coding Dictionary

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 15.1). Prior and concomitant medicationswill be coded using the March 2013 version of the World Health Organization (WHO) Drug Dictionary.

## 5.4 Analysis Visit Window, Time Periods and Missing Values

### 5.4.1 Visit Windows for Clinical Rating Scales

For clinical rating scales (e.g. SAPS associated scores, CGI associated scores and CBS) measured between first dose date and last dose date + 3, data will be summarized using the derived visit based on the visit windows shown in Table 1.

Nominal visits as specified in Appendix A will be re-assigned to the derived visits. The re-assigned visit will be referred to as the 'derived visit' as identified in Table 1 below. After reassignment of a visit, if there are multiple assessments for the same visit, the assessment nearest to the target study day will be kept for analysis. In the event of a tie, the assessment from the earlier study day will be kept for analysis. Unscheduled visits are included in the visit re-assignment.

**Table 1. Visit Assignments for Clinical Rating Scales Assessments**

| Derived Visit | Target Study Day* | Time Interval (Study Day Range) |
|---|---|---|
| Baseline (Day 1) | 1 | Last value on or before the first dose |
| Week 2 | 15 | 2 – 21 |
| Week 4 | 29 | 22 – 42 |
| Week 12 | 85 | 43 – 126 |
| Week 24 | 169 | 127 – 210 |
| Week 36 | 253 | 211 – 294 |
| Week 48 | 337 | 295 – 421 |
| Week 72 | 505 | 422 – 589 |
| Week 96 | 673 | 590 – 757 |
| Week 120 | 841 | 758 – 925 |
| Week 144 | 1009 | 926 – 1093 |
| Week 168 | 1177 | 1094 – 1261 |
| Week 192 | 1345 | 1262 – 1429 |
| >Week 192 | 1513 | 1430 and up |

*Target study day is relative to date of first dose in the ACP-103-015 study.

The study day is defined as:

For visits on or after the reference day: study day = visit day – reference day +1

For visits before the reference day: study day = visit day – reference day where the reference day equals the start day of study drug in the ACP-103-015 study.

### 5.4.2 Summary Time Periods for Safety Results

For safety assessments (AEs, laboratory tests, vital signs, ECG data, UPDRS II+III and physical examinations), the data summary will be based on chronological time periods as defined in Table 2. Rules for determining the analysis values within each time period are detailed in Section 5.13.

**Table 2. Safety Summary Time Periods**

| Time Period | Study Day Range | |
|---|---|---|
| | AE Onset | Other Safety Measurement |
| Baseline | N / A | Last value on or before the first dose |
| First 4 weeks | 1* - 28 | 2* - 28 |
| 1 – 3 months | 29 – 91 | 29 – 91 |
| >3 – 6 months | 92 – 183 | 92 – 183 |
| >6 – 12 months | 184 – 365 | 184 – 365 |
| >1 – 2 years | 366 – 730 | 366 – 730 |
| >2 – 3 years | 731 – 1095 | 731 – 1095 |
| >3 – 4 years | 1096 – 1461 | 1096 – 1461 |
| >4 years | >= 1462 | >= 1462 |

* Protocol procedures specified that all baseline assessments were to be done before administration of study drug on Day 1. For conservative reason, AEs started on Day 1 are considered “post-baseline”.

### 5.4.3 Missing Values

Unless otherwise specified, missing values will not be imputed for any of the rating scales or questionnaires. A missing value is defined as one which is blank, not done, or not applicable on the eCRF. If a scale has a “Not Assessed” response, then that value will be considered a missing value for analysis. In addition, if one or more items in a given subscale is missing then the entire subscale will be set to missing. In case a questionnaire consists of more than 1 subscale, any non-missing subscales will be used for analysis. For example, if in the SAPS scale the Hallucination subscale has a missing item, but the Delusion subscale is complete, then the Delusion subscale will be analyzed per the analysis plan. For the CGI-S and CGI-I questionnaires, a response of “Not assessed” will be treated as a missing value as well.

For questionnaires that utilize a total score (NMSS, Caregiver Burden Scale), if any of the individual items that contribute to the total score are missing, the total score will also be set to missing.

Missing baseline assessments will not be imputed. However, the SAPS and CGI-S scales were not collected at the ACP-103-015 baseline; therefore, the last core study assessment will serve as the ACP-103-015 baseline assessment for these scales.

Missing dates for AEs and concomitant medications will be imputed for the purpose of establishing the time of event in relation to study treatment. All data listings will display data as reported on the eCRF. When AE onset date or concomitant medication dates are missing or incomplete, the study days (onset or start day relative to first dose date) will be calculated based on imputed value.

The imputation rules for AE/concomitant medication start dates are as follows:

- If a full date is missing, impute date as date of first dose (study day 1);

- If the day component is missing from full date, date is imputed as study day 1 if the date is in the same month and year as first dose, otherwise impute as the 1st of the month;
- If the month and day components are missing from full date, but year is present, the date is imputed as January 1 if the year is different than the year of first dose, or imputed as the first dose date if the year is the same as the year of first dose;
- If any of the above imputations result in a start date which is later than an existing complete end date, the start date will be set equal to the end date.

Missing end dates for AE will not be imputed.

The imputation rules for concomitant medication end date are as follows:

- If a full date is missing and the status of the medication is not ongoing, impute date as the last dose date;
- If the day component is missing from full date, impute date as the last day of the month;
- If the month and day components are missing from full date, but year is present, the date is imputed as last dose date if the year is the same as the last dose date and medication start date is prior to last dose date, otherwise impute as the last day of the year;
- If any of the above imputations result in the medication end date which is prior to the medication start date, the medication end date will be set equal to the medication start date.

For AE listing, AEs missing severity or relationship will be displayed as missing to reflect the raw data collected on eCRF. For AE summary by severity, AEs with a missing severity will be tabulated as “severe”. AEs with missing relationship will be tabulated as related.

The last dose date is collected on the discharge eCRF. If a subject has withdrawn from the study, but the last dose date is reported as a partial date, then the last dose date will be imputed using logical algorithms utilizing other reported data (e.g. death date if died, AE end date if discontinued due to AE, maximum projected dose date based on last dispensed and returned tablets, database snapshot date, …etc). The complete programming algorithms are detailed in a separate programming specification document.

## 5.5 Subject Enrollment and Disposition

Subject enrollment by protocol amendments and subject counts by study center and prior study will be summarized.

A summary of subject disposition will display the number of subjects enrolled, received study drug, and remained in the study (using visit dates recorded on the vital signs CRF) at the beginning of the following time periods: first 4 weeks (Study Days 1 to 28), 1 to 3 months (Study Days 29 to 91), >3 to 6 months (Study Days 92 to 183), >6 month to 1 year (Study Days 184 to 365), >1 to 2 years (Study Days 366 to 730), >2 to 3 years (Study Days 731 to 1095), >3 to 4 years (Study Days 1096 to 1461) and >4 years (Study Days >=1462). Also included in this summary will be subject discontinuations showing the number of subjects who terminated from the study according to the reason for study termination/discontinuation (Investigator reported and Sponsor re-classified). Reasons for study termination will also be summarized by the time period specified above.

The withdrawal reasons as reported by the investigators on the eCRF are:

- Adverse event
- Death
- Disease progression
- Subject's voluntary withdrawal of consent (Voluntary withdrawal of consent)
- The Investigator determines that continuation in the study would be detrimental to a subject's well-being because of development of a serious illness, any other significant change in clinical status, or any other compelling medical reason (Investigator decision)
- Subject fails to comply with protocol requirements (Subject non-compliance)
- Lost to follow-up
- At discretion of Sponsor (Sponsor decision)

To better understand the discontinuation pattern, ACADIA reviewed the withdrawal reasons and in some cases, on the basis of verbatim comments in the eCRF, re-classified the reasons for discontinuation using the following categories:

- Adverse event
- Death
- Lack of efficacy / PDP progression
- PD /Concomitant disease progression
- Voluntary withdrawal of consent
- PDP improvement
- Investigator decision
- Subject non-compliance
- Lost to follow-up
- Sponsor decision

Subject disposition and study completion by Investigator-specified and Sponsor-reclassified reasons for termination will be presented in data listings and summary tables. Dispositions will also be summarized by 3 regions: North America (US and Canada), Europe and India.

## 5.6 Core Study Information

The core (preceding) study information (studies ACP-103-012, ACP-103-014, and ACP-103-020) will be summarized by protocol and will also be presented in a data listing.

## 5.7 Study Drug Exposure and Overall Compliance

### 5.7.1 Study Drug Exposure

For the final CSR, all subjects' study drug (pimavanserin) exposure will be calculated as last dose date minus first dose date + 1. For the interim report(s), the drug exposure will be censored at the database snapshot date for the on-going subjects. For example, if a subject had withdrawn from the study before the database snapshot, then the exposure duration for this subject is last dose date minus first dose date + 1; if a subject was still ongoing at the database snapshot date, then the exposure duration for this subject is database snapshot date minus first dose date + 1.

A summary of study drug exposure will include the duration of exposure as a continuous measure in days and a categorical measure for the intervals (1-28 days, 29-91 days, 92-183 days, 184-365 days, 366-730 days, 731-1095 days, 1096-1461 days, ≥1462 days). Total amount of administered pimavanserin (mg) will be estimated by (duration of exposure*40 mg). Study drug exposure by Sponsor re-classified termination reasons will also be summarized. Study drug exposure for subjects who died will also be summarized.

Study drug exposure measures as described above will be presented in a listing.

Since this is an open-ending study, time on pimavanserin treatment (time on study) will be evaluated for all subjects and by subgroups: baseline age group (≤75 years old or >75 years old), gender (female or male), and geographic area (North America or outside North America). For subjects who have discontinued from study, the days on pimavanserin treatment in study -015 (not counting the exposure duration from the preceding study) will be calculated as last dose date minus first dose date + 1; otherwise the time on study will be censored at database snapshot date and will be calculated as database snapshot date minus first dose date + 1. Kaplan-Meier estimates of percent subjects on treatment at 6 months (183 days), 1 year (365 days), 1.5 years (548 days), 2 years (730 days), 2.5 years (913 days), 3 years (1095 days), 3.5 years (1278 days) and 4 years (1461 days), as well as median days on treatment will be presented.

In addition, Kaplan-Meier estimates percent subjects free of AEs leading to study termination or drug withdrawal and median days to due to AEs leading to study termination or drug withdrawal will be summarized for all subjects and by

aforementioned subgroups. For this analysis, if a subject has an AE leading to study termination or drug withdrawal, the time to event will be calculated as last dose date minus first dose date + 1; otherwise the time to event will be censored at either last dose date (for subjects who discontinued due to reasons other than AE) or database snapshot date (for ongoing subjects).

## 5.8 Important Protocol Deviations

Protocol deviation logs will be reviewed and the deviations will be categorized by deviation type and grouped as major or minor.

A summary of the number and percentage of subjects with major deviations by deviation category will be provided. A listing of major protocol deviations by site and subject will also be provided.

## 5.9 Analysis of Demographic and Baseline Characteristics

### 5.9.1 Demographics and Baseline Characteristics

Demographic data (age at 015 first dose date, sex, and race) will be summarized for all subjects for the safety analysis set using descriptive statistics. Summary of age categories (<65, 65-75, and >75 years) will also be presented. Race/ethnicity will be presented as White, Black, Asian and other. Region will be presented as North America (US and Canada), Europe, and India. In addition, subject counts from 2 geographic areas, North America and outside North America (Europe and India combined) will also be presented since the number of subjects (N=18) in India was too small to make meaningful comparisons. The geographic areas will be used for summarizing the clinical rating scales (Section 5.11) or mortality (Section 5.13.2).

Demographic information as described above, along with childbearing status, method of birth control for subjects of childbearing potential, and date of birth will also be presented in a data listing.

Baseline characteristics will include weight (kg), height (cm), BMI ($kg/m^2$), and questionnaire scores for SAPS-PD, SAPS-H+D, SAPS-H, SAPS-D, UPDRS II+III, UPDRS II, and UPDRS III. These parameters will be summarized with descriptive statistics. For the questionnaire scores the last value from the core study will serve as the baseline value of the current study. Each of these parameters will also be presented in a data listing.

### 5.9.2 Prior, Post and Concomitant Medications

Medications started prior to the day of the first dose of open-label study medication and continued into the study, or medications started on or after the day of the first dose of study medication and before or on the day of the last dose of the study medication will be reported as concomitant medications. Medications stopped before the first date of study medication dosing will be considered prior medications. Medications started after

the day of last dose of study mediation will be considered post-treatment. Prior, concomitant and post-treatment medications will be listed.

The number and percentage of subjects using concomitant medications in each WHO Drug Anatomical/Therapeutic/Chemical (ATC) Level 3 (i.e., pharmacological subgroup) category and preferred term will be summarized. Separate summaries will be presented for

- Anti-psychotic medications
- Medications indicated for dementia
- Medications indicated for motor function
- Medications not included in the preceding 3 categories.

Number of concomitant medications will be summarized at first dose date and last dose date for overall, indicated for motor functions, dementia and antipsychotics. Antipsychotics taken post-treatment (medication started after the last dose date) will also be summarized. Multiple medications for the same subject may be classified to the same ATC level or preferred name. However, subjects will only be counted once for each level of classification.

Prior, concomitant, and post-treatment medications with the verbatim, ATC level 3 category, preferred term, indication, dosage, route, unit, frequency, and start/stop dates of administration will be provided in a listing.

### 5.9.3 Medical History

A listing of the body system, verbatim condition/abnormality/procedure, date of onset, and an indicator for whether or not the condition is still present at baseline will be provided. A summary table will also be provided.

## 5.10 Analysis of Pharmacokinetic Data

For the final clinical study report, pimavanserin plasma concentration data will be listed by subject with derived visit, most recent pimavanserin dose date and time, and PK sample collection date and time. No summary table will be generated.

## 5.11 Analysis of Clinical Rating Scales

### 5.11.1 Scale for the Assessment of Positive Symptoms

The Scale for the Assessment of Positive Symptoms (SAPS) was designed to measure positive psychotic symptoms. Positive symptoms include delusions, hallucinations, abnormalities in language and behavior, and disordered thought processes. Two of the SAPS subscales, Hallucinations and Delusions, will be administered in this trial as a 20-item assessment. The SAPS Hallucinations scale contains 7 items and the Delusions scale contains 13 items. The score for each item ranges from 0 to 5 (0 = absent, 1 =

questionable, 2 = mild, 3 = moderate, 4 = marked, 5 = severe). The last item of each scale is the "Global rating of severity" for the corresponding domain. The combined score for SAPS-H+D will be derived as the sum of the 20 items, including the global ratings. Possible scores range from 0 to 100. If one or more of the 20 items is missing, the combined score is considered as missing at the visit. The SAPS questionnaire will be administered at the Month 1 (Week 4) visit only. Note that the baseline SAPS scores were measured at the end of preceding study.

Nine of these 20 items from the SAPS Hallucinations and Delusions domains were found to be more prevalent in PDP subjects with more severe symptoms and therefore these items are expected to have improved clinical relevance and face validity. This PD-adapted version of the SAPS (SAPS-PD; Voss et al., 2013) includes these 9 items:

- H1 Auditory Hallucinations;
- H3 Voices Conversing;
- H4 Somatic or Tactile Hallucinations;
- H6 Visual Hallucinations;
- H7 Global Rating of Severity of Hallucinations;
- D1 Persecutory Delusions;
- D2 Delusions of Jealousy;
- D7 Ideas and Delusions of Reference;
- D13 Global Rating of Severity of Delusions.

The SAPS-PD (9-item sum score), SAPS-H+D (20-item sum score), SAPS-H (hallucination subscale sum score), and SAPS-D (delusion subscale sum score) data will be summarized for all subjects and by geographic area (North America or outside North America) and by prior treatment (placebo, pimavanserin 10 mg, pimavanserin 20 mg, or pimavanserin 40 mg). Within North America, the SAPS-PD data will also summarized by prior treatment.

The GSAPS-H+D (sum score of global rating of hallucination severity and global rating of delusion severity), GSAPS-H (global rating of hallucination severity), and GSAPS-D (global rating of delusion severity) data will be summarized for overall subjects.

The SAPS-PD, SAPS-H+D, SAPS-H, SAPS-D, GSAPS-H+D, GSAPS-H, GSAPS-D, and SAPS individual item scores will be presented in listings.

### 5.11.2 Caregiver Burden Scale

The Caregiver Burden Scale (CBS) is a 22-item questionnaire completed by the subject's caregiver. Each item is rated on a scale of 0 - 4 where 0 = never, 1 = rarely, 2 = sometimes, 3 = frequently, 4 = nearly always. The total score of the Caregiver Burden Scale will be derived as the sum of the 22 items, with a possible range of 0 to 88. The total score and change from baseline will be summarized by visit. The data will also be summarized within each geographic area (North America and outside North America).

### 5.11.3 Clinical Global Impressions - Severity

The CGI-Severity (CGI-S) is a single-item score from a 7-point rating scale used to assess the investigator's global impression of severity of psychosis as it relates to this study population. Scores range from 1 (Normal, not at all ill) to 7 (Among the most extremely ill patients). Scores of 0 indicate 'Not Assessed' and will be converted to missing. The CGI-S will be performed at each post-baseline study visit.

The observed values of CGI-S will be summarized for each study visit. The data were also summarized within each geographic area (North America and outside North America).

### 5.11.4 Clinical Global Impression – Improvement

CGI-Improvement (CGI-I) is a single-item score from a 7-point rating scale assessed only at post-baseline visits and is used to assess the improvement in subjects' overall psychotic condition. The 7-point scale ranges from 1 (Very much improved) to 7 (Very much worse). Scores of 0 indicate 'Not Assessed' and will be converted to missing.

The observed values for Clinical Global Impression of Improvement (CGI-I) will be summarized by visit. Additionally the proportion of CGI-I responders [with responder defined as a subject with a score of 1 (very much improved) or 2 (much improved)] will be summarized by visit. A CGI-I rating of 1 (very much improved) or 2 (much improved) represents the point at which clinically meaningful improvement in psychotic symptoms would be expected.

The observed mean values and the CGI-I responders data will also be summarized within each geographic area (North America and outside North America).

### 5.11.5 Resource Utilization in Dementia Scale – Lite

RUD-Lite, a health economics measure, will be collected at baseline, Month 12 and every 6 months thereafter. The individual item scores will be presented in a data listing. Additional analyses may be conducted and reported separately.

## 5.12 Interim Analyses and Data Safety Monitoring Board

To provide an adequate update of the long-term safety profile for pimavanserin's new drug application (NDA) submission, a data snapshot was taken on 13DEC2013 and an interim analysis will be performed.

There is no Data Safety Monitoring Board (DSMB) for this study. Safety data are monitored throughout the study and aggregate safety reports are produced and reviewed approximately quarterly.

## 5.13 Analysis of Safety Data

All safety data summaries will be based on the safety analysis set.

### 5.13.1 Adverse Events

AEs started between first study dose date and 30 days after the last dose date will be considered treatment-emergent AE (TEAEs). Any AEs with a completely missing start date will be considered as TEAEs. All AEs and TEAEs will be summarized. In addition, the number of TEAEs, and the number and percent of unique subjects with TEAEs will be summarized by system organ class (SOC) and preferred terms. For SAEs, the SAE onset date will be used in place of the AE onset date for the determination of treatment-emergent status and for assignment of the event to time windows and onset age groups.

AEs will be summarized in terms of the proportion of subjects as well as number of events. When calculating the proportion of subjects with AEs by time period or age groupeach subject will be counted in the numerator at most once and any repetitions will be ignored; the denominator will consist of all safety-evaluable subjects in the specified time period or age group. When calculating the number of events, each unique record in the database will be counted once.

Additional summaries of TEAEs will also be tabulated with respect to severity (mild, moderate, severe) and AEs of special interest. Tabulations will also be provided for AEs by maximum severity where a subject with more than one event coded to the same preferred term will be classified according to the most severe event. Similarly, in the tabulation by strongest relationship, a subject will be classified according to the event with the strongest relationship to study drug.

An overall summary of all AEs and TEAEs will be presented. The number and percent of unique subjects with TEAEs will be summarized by system organ class (SOC) and preferred term. The number and percent of unique subjects with TEAEs that are determined by investigators as related (possibly, probably, or definitely) to study drug will also be summarized by SOC and preferred term. Additional summaries of TEAEs will also be tabulated with respect to severity (mild, moderate, or severe), where a subject with more than one event coded to the same preferred term will be classified according to the more severe event. A summary of TEAEs in descending order of frequency by preferred term will also be tabulated. Listings of deaths, serious AEs and AEs leading to study treatment discontinuation will also be provided.

The tabulation of TEAEs will be grouped by (1) time period at AE onset and (2) age at AE onset.

(1) AEs grouped by time period at AE onset: For all TEAEs, serious TEAEs, TEAEs leading to discontinuation of study drug, and TEAEs of special interest (those that may be expected on the basis of pimavanserin's pharmacology, those of special regulatory interest [suicidality, abuse liability etc], and those commonly associated with current antipsychotics), the count and percentage of subjects will be summarized by time period defined in Section 5.4.2 Table 2. The denominator for a time period will be the number of subjects on treatment

(including a 30-day follow-up) during that particular time period. TEAEs with fatal outcome will be summarized by time period at death.

(2) AEs by age group at AE onset: For all TEAEs, serious TEAEs, TEAEs leading to discontinuation of treatment, and TEAEs of special interest, the count and percentage of subjects will be summarized by age category at the time of AE onset. Age at onset will be categorized as follows: ≤ 50 years, 51 - 60 years, 61 – 70 years, 71 – 80 years and 81 - 90 years. The denominator for an age group will be the number of subjects on treatment (including a 30-day follow-up) while in that particular age group. TEAEs with fatal outcome will be summarized by age group at death.

An AE listing by subject will display all events and will include the verbatim term in addition to the MedDRA SOC and preferred term. This listing will also include all relevant CRF data associated with the event: date of onset , date of last dose, severity, outcome, relationship to study drug, action taken, and seriousness.

In addition, AE tables also will be summarized by age group and onset time period for subject with concomitant antipsychotic use and without antipsychotic use.

### 5.13.2 Deaths and Other Serious and Significant Adverse Events

Treatment-emergent SAEs, TEAEs leading to discontinuation from the study or study drug, and TEAEs with fatal outcome will be summarized by time period as given in Table 2 in frequency tables by SOC and preferred term. In addition, the overall AE summary table will also be presented for all events (i.e. treatment-emergent plus non-treatment-emergent events).

Subject listings of SAEs, deaths, and AEs leading to discontinuation of study drug will be provided. These listings will provide all relevant eCRF data for each event including the date/study day of onset, date/study day resolved, date of last dose/study day of last dose, severity, outcome, relationship to study drug, action taken, and seriousness.

Kaplan-Meier estimates of percent surviving subjects at 6 months, 1 year, 1.5 years, 2 years, 2.5 years, 3 years, 3.5 years and 4 years, as well as median survival time will be computed for all subjects and by subgroups: baseline age group (≤75 years old or >75 years old), gender (female or male), and geographic area (North America or outside North America). If a subject is deceased, the survival time will be calculated as death date minus first dose date + 1; otherwise the survival time will be censored at the last dose date (for subjects who have discontinued from the study) or database snapshot date (for ongoing subjects).

### 5.13.3 Clinical Laboratory Data

Observed clinical laboratory data and change from baseline values will be summarized by time period for hematology, chemistry and numeric urinalysis using the periods specified in Section 5.4.2 Table 2. For each laboratory parameter collected for each subject, within each time period, 2 different representations will be used for generating

the population summary statistics: the highest and lowest measurement from that subject during that particular time period. The highest or lowest measurement will capture the worst or the most extreme observed value (depending on the laboratory test, the highest or lowest or both can be concerning). In addition to each time period, for each laboratory parameter, the last, highest and lowest measurement collected for each subject during the entire study period will also be summarized.

For a subset of clinical laboratory parameters (red blood cell count, hemoglobin, white blood cell count, neutrophils, alkaline phosphatase, alanine aminotransferase , aspartate aminotransferase , bilirubin (total), gamma-glutamyl transferase, creatine phosphokinase, lactate dehydrogenase, blood urea nitrogen, creatinine, and uric acid) low [L], normal [N] or high [H] status will be determined based on the normal ranges provided by the testing laboratory.

The count and percentage of subjects with markedly abnormal post-baseline clinical laboratory parameters tabulated for all subjects and a subset of subjects with normal baseline will also be presented by time period and overall as defined in Table 2 and for overall study period. The criteria for markedly abnormal laboratory values are provided in Appendix B. For each laboratory parameter, within each specified time period and for overall study period, if a subject has at least 1 measurement meeting the marked abnormal criterion, this subject will be counted as having an incidence. The denominator for each laboratory parameter within each specified time period will be the total number of subjects with baseline and at least 1 post-baseline value within that particular time period.

Clinical laboratory data will be displayed in data listings with date and study day of collection. All units will be displayed according to the Système International (SI) conventions for units. Out-of-range values will be flagged in the data listings (i.e., 'L' or 'H').

The routine laboratory panel includes:

Hematology

Complete blood count including White Blood Cell Count, Complete Differential (Relative and Absolute), Hematocrit, Hemoglobin, Red Blood Cell Count, Platelets, and Reticulocyte Count.

Clinical Chemistry

Sodium, Potassium, Chloride, Phosphorus , Calcium, Carbon dioxide, Blood urea nitrogen, Creatinine, Uric acid, Alanine Aminotransferase, Aspartate Aminotransferase, Gamma-Glutamyl Transferase, Alkaline Phosphatase, Total Bilirubin, Lactate Dehydrogenase, Albumin, Total Protein, and Creatine Kinase/Creatine Phosphokinase.

Urinalysis

Blood, Red Blood Cells, White Blood Cells, Protein, Glucose, Ketones, Specific Gravity, and pH (only the pH and specific gravity information was presented in the summary table; all urinarlysis data was presented in a listing)

### 5.13.4 Vital Signs and Weight

#### 5.13.4.1 Vital Sign Parameters

Vital signs are collected at every study visit. A summary of observed values and change from baseline by time period will be presented for orthostatic blood pressure (systolic and diastolic in mmHg) and pulse (beats per minute), measured supine (after 5 minute), and standing (after 1 minute), respiratory rate, oral temperature and weight. For each vital sign parameter collected for each subject, within each time period, 2 different representations will be used for generating the population summary statistics: the highest and lowest measurement. The highest or lowest measurement will capture the worst or the most extreme observed value. In addition to each time period, for each vital sign parameter, the last, highest and lowest measurement collected for each subject during the entire study period will also be summarized.

All observed and change from baseline vital sign values will be provided in a listing with date of collection, study day, and time period.

#### 5.13.4.2 Orthostatic Hypotension

Orthostatic hypotension is assessed each time vital signs are collected for pulse and blood pressure through the comparison of 5 minute supine results against 1 minute standing. The count and percentage of subjects experienced orthostatic hypotension as defined below will be summarized for each time period defined in Section 5.4.2 Table 2 and for overall study period (at any timepoint postdose) for subjects for whom orthostatic hypotension was not present at baseline. If a subject has at least 1 measurement meeting the orthostatic hypotension criteria during a given time period, this subject will be counted as having an incidence for that time period. The denominator for percentages is the number of subjects with non-missing data at each visit.

Orthostatic hypotension occurs if:

- there is a decrease of ≥20 mmHg in systolic blood pressure (SBP)

OR

- there is a decrease of ≥15 mmHg in diastolic blood pressure (DBP)

OR

- there is an increase of ≥20 bpm in pulse rate (PR);

each measured from 5 minutes supine to 1 minute standing at the same visit.

An overall count and percentage of subjects experienced orthostatic hypotension based on findings from either AE records (i.e. where the preferred term = ‘Orthostatic

hypotension') or vital signs (orthostatic changes in blood pressure and pulse) will also be presented. Data listing of blood pressure and pulse measurements for these subjects will also be presented.

#### 5.13.4.3 Weight

Body mass index (BMI) is calculated from height and weight recorded at each visit. Observed values in weight (kg) and BMI (kg/$m^2$) will be summarized with descriptive statistics by time period as defined in Section 5.4.2 Table 2. Within each time period: the highest and lowest measurement from each subject will be summarized. In addition to each time period, the last, highest and lowest measurement collected for each subject during the entire study period will also be summarized.

In addition, a summary table of clinically meaningful weight change will be provided by time period and overall (any timepoint postdose). Two criteria will be applied and tabulated separately: (1) weight increase or decrease $\geq$ 7% from baseline; or (2) a BMI <19 or >32 kg/$m^2$. Within each time period if a subject has at least 1 measurement meeting the criterion, this subject will be counted as having the incidence for that time period. The denominator for percentages is the number of subjects with non-missing data within each time period.

All observed values for height, weight, and BMI will be provided in a listing with date of collection, study day, and time period. Subjects with a clinically meaningful weight change from baseline will be identified.

### 5.13.5 Electrocardiogram (ECG)

#### 5.13.5.1 ECG Parameters and Corrected QT (QTc)

Observed and change from Baseline values for each time period as defined in Section 5.4.2 Table 2 will be summarized with descriptive statistics for QT, corrected QT (QTcF and QTcB), heart rate, PR Interval, R-R Interval, and QRS Interval. If a subject did not have a baseline ECG assessment, then the last available ECG from the core study will be used as the ACP-103-015 baseline value. For each ECG parameter collected for each subject, within each time period, 2 different representations will be used for generating the population summary statistics: the highest and lowest measurement. The highest or lowest measurement will capture the worst or most extreme observed value. In addition to each time period, for each ECG parameter, the last, highest and lowest measurement collected for each subject during the entire study period will also be summarized. In addition, ECG parameters will also be summarized from pre-PIM baseline and change from pre-PIM baseline. The definition of pre-PIM baseline is: for subjects who received pimavanserin in prior studies, baseline value is obtained from prior-study baseline (pre-exposure); for all other subjects, study -015 baseline is used.

Bazett's corrected QT will be calculated using the formula QTcB = QT/ $\sqrt[2]{RR}$.
Fridericia's corrected QT will be calculated using the formula QTcF = QT/ $\sqrt[3]{RR}$.

An additional summary of the proportion of subjects with values of normal or abnormalfor each parameter and time period as described above will be provided. Table 3 below lists ECG parameter normal ranges. The proportion of subjects with treatment-emergent abnormally high or abnormally low values will also be presented by time period and overall (at any timepoint postdose).

**Table 3. ECG Parameter Normal Ranges**

| ECG Parameter (unit) | Normal Range |
|---|---|
| QRS Interval (msec) | 60 – 100 |
| QTcF (msec) | <500 |
| QTcB (msec) | <500 |
| QT Interval (msec) | 360 – 470 |
| PR Interval (msec) | 120 – 200 |
| R-R Interval (msec) | 550-1500 |
| Heart Rate (beats per min) | 40 – 110 |

The proportion of subjects with QTcF ≤ 450 msec, 451 - ≤ 480 msec, 481 - ≤ 500 msec and > 500 msec, and QTcF change from Baseline <10 msec, 10 - 29, 30 - 59 msec, and ≥ 60 msec will be summarized by time period and overall (at any timepoint postdose). For each ECG parameter, within each specified time period, if a subject has multiple results, the worst (longest interval) measurement within the time period will be used as the analysis value.

All summaries will also be performed in subgroups by gender.

Listings of the ECG parameters, including QTcB, as described above will include date and time of collection, observed values, and flag indicators for any value outside of the normal range (L for below normal, H for above normal).

#### 5.13.5.2 ECG Overall Interpretation

The ECG interpretation (normal, abnormal not clinically significant [NCS], abnormal clinically significant [CS]) will be summarized for each time period and overall. Within each time period if a subject has at least 1 clinically significantly abnormal record, this subject will be counted as having the incidence for that time period. The ECG parameters for these subjects will be presented in a data listing.

The ECG interpretation will also be provided in a listing with date and time of collection and additional comments.

### 5.13.6 UPDRS Parts II and III

The Parts II+III UPDRS score will be derived as the sum of the 40 items from activities of daily living (Part II, 13 items) and motor examination (Part III, 27 items), with a range of 0 to 160 (for each item the score ranges from 0 (normal or absent of symptom) to 4 (worst condition)).

For UPDRS Parts II+III, Part II, and Part III scores, the highest (worst) measurement will be used for generating the population summary statistics within each time period. In addition, for the overall study period, the last and the highest measurement from each subject will be summarized.

### 5.13.7 Non-Motor Symptom Scale

The Non-motor Symptoms Scale (NMSS) is a 32 item scale that measures non-motor symptoms of PD. NMSS contains nine domains: cardiovascular including falls (2 items), sleep/fatigue (5 items), mood/cognition (7 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary (3 items), sexual function (2 items), and miscellaneous (4 items). Each item has a severity rating (0 to 3) and a frequency rating (1 to 4). The score for each item is the product of severity and frequency with a range or 0 to 12. NMSS total score is the sum of the 32 item scores, ranging from 0 to 384.

The NMSS individual item scores, along with the total score, will be presented in a data listing by domain. The NMSS was initially collected during this study, but was discontinued with Amendment No. 6.

### 5.13.8 Physical Examination

Physical examination results (normal, abnormal) will be summarized in a frequency table by body system by time period.

Data listings will include date and time of evaluation, any abnormal findings within each body system, clinical significance, and a comment describing the abnormality and clinical significance of the abnormality.

## 5.14 Additional Data Presentations

### 5.14.1 Protocol Amendments

Study enrollment started with the original Protocol. The number and percent of subjects who consented to the original Protocol, Amendment 1, Amendment 2, Amendment 3, Amendment 4, Amendment 5, Amendment 6, and any potential future Amendments of the protocol will be summarized in a table.

Subjects' consent to protocol amendments will also be presented in a data listing.

### 5.14.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria will be provided in separate data listings, ordered by protocol amendment. Violations of inclusion and exclusion will be listed by protocol amendment and subject. Waivers to the inclusion and exclusion criteria will be listed by site and subject.

### 5.14.3 Serum Pregnancy

Pregnancy tests (females only) are performed on serum with results recorded in the eCRF. A listing of all qualitative pregnancy test results (positive, negative) will be provided with date and study day of collection.

### 5.14.4 Phone Contact

Documentation of phone contact with the subject to assess tolerability, as reported on the eCRF, will be presented in a data listing along with reason for no contact, if applicable.

## 6 DEVIATIONS FROM PROTOCOL PLANNED ANALYSIS

Section 10.1 of the Protocol specified that all analyses would be performed SAS® using version 8. However, SAS® version 9.3 (or higher) will be used for all statistical analyses.

## 7 VALIDATION OF SAS® CODE

All SAS® programs used in the production of statistical analyses, analysis datasets, tables, listings, and figures will be validated by independent programming prior to finalization or with a peer review of the SAS® log files. In addition, all program output will be independently reviewed. The validation process will be used to confirm that statistically valid methods were implemented and that all data manipulations and calculations were accurately performed.

## REFERENCES

ACP-103-015 Clinical Study Protocol Amendment 6, Acadia Pharmaceuticals Inc. 30 June 2010.

ICH Guidance E3 – Structure and Content of Clinical Study Reports.

Voss T, et al. (2013), Performance of a shortened Scale for Assessment of Positive Symptoms for Parkinson's disease psychosis, *Parkinsonism and Related Disorders* 19(3), 295-9.

## APPENDIX A: Schedule of Events

| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| | Baseline [1] (Day 1) | Week 2 Day 14 ± 3 days | Month 1 Day 28 ± 3 days | Month 3 Day 84 ± 7days | Month 6 Day 168 ± 7days | Month 9 Day 252 ± 7days | Month 12 (Day 336 ± 7 days) AND every 6 months thereafter (168 days ± 7 days) | End-of-Study (if subject withdraws or is terminated from the study) |
| Informed Consent | X | | | | | | | |
| Medical History | X[2] | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | |
| Weight | X | X | X | X | X | X | X | X |
| ECG | X | X | X | X | X | X | X | X |
| Vital Signs | X | X | X | X | X | X | X | X |
| Physical Exam[3] | X | X | X | X | X | X | X | X |
| Clinical Labs | X | X | X | X | X | X | X | X |
| Serum Pregnancy Test | X | | | X | X | X | X | X |
| Plasma PK Sample[4] | | X | X | X | X | X | X | X |
| Caregiver Burden Scale | | X | X | X | X | X | X | X |

[1] Subjects that enroll in this study within one week of completion from a previous blinded study of pimavanserin in will only be required to sign an informed consent form, complete an update to the medical history that was performed during the screening and baseline visit of the previous study, complete the Baseline RUD-Lite, and receive study drug during the baseline visit. Subjects that enroll greater than one week of completion from the previous blinded study will be required to complete ALL baseline assessments. All assessments are to be performed PRIOR to investigational drug administration.

[2] The medical history to be taken at baseline will be an update to the medical history taken during the screening and baseline visits of the previous study. Any AEs that occur after the informed consent is signed and before the first dose of investigational drug is taken are to be recorded in the updated medical history and NOT in the AEs log.

[3] The physical examination performed on Week 2, Month 1, Month 3, Month 6, Month 9, Month 12 and every 6 months thereafter will be an update to the full physical examination conducted during either the last visit of the previous study or at Baseline of this study.

| Visit | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| | Baseline (Day 1) | Week 2 (Day 14 ± 3 days) | Month 1 (Day 28 ± 3 days) | Month 3 Day 84 ± 7days | Month 6 Day 168 ± 7days | Month 9 Day 252 ± 7days | Month 12 (Day 336 ± 7 days) AND every 6 months thereafter (168 days ± 7 days) | End-of-Study (if subject withdraws or is terminated from the study) |
| SAPS[5] | | | X | | | | | |
| UPDRS Parts II & III[6] | | X | X | X | X | X | X | X |
| CGI-S and CGI-I[7] | | X | X | X | X | X | X | X |
| Adverse Events[8] | X | X | X | X | X | X | X | X |
| RUD-Lite[1, 9] | X | | | | | | X | X |
| Prior/Con Meds | X | X | X | X | X | X | X | X |
| Investigational Drug Administration[10] | X | X | X | X | X | X | X | |

[4] Plasma samples for determination of pimavanserin levels are to be taken PRIOR to investigational drug administration on study days; on study visit days the subject should NOT take the day's dose of investigational drug at home. They should wait until they are at the clinical site.

[5] Scale for the Assessment of Positive Symptoms (SAPS) may be administered by a Central Rater Service.[redacted]

[6] Unified Parkinson's Disease Rating Scale (UPDRS)

[7] Clinical Global Impression scale-Severity (CGI-S) and Clinical Global Impression scale-Improvement (CGI-I)

[8] Any adverse event that occurs after signing the ICF and before the first dose of investigational drug is to be recorded in the updated Medical History taken on the Baseline visit (Day 1).

[9] Subjects will complete the Baseline RUD-Lite at the Baseline Visit and the Follow Up Visit at subsequent visits, where noted.

[10] Investigational drug is to be taken daily; on study visit days subjects should NOT take the day's dose at home but should wait until they are at the site and have had blood drawn for pimavanserin plasma level determination before taking the day's dose.

# APPENDIX B: Criteria for Markedly Abnormal Laboratory Values in SI (Système International) Units

| Lab Analyte | Criteria |
|---|---|
| **Chemistry** | |
| Aspartate aminotransferase (AST) | ≥ 3 x upper limit of normal |
| Alanine Aminotransferase (ALT) | ≥ 3 x upper limit of normal |
| Alkaline Phosphatase | ≥ 3 x upper limit of normal |
| Lactate Dehydrogenase (LDH) | ≥ 3 x upper limit of normal |
| Blood Urea Nitrogen (BUN) | ≥ 10.71 mmol/L |
| Creatinine | ≥ 176.8 µmol/L |
| Uric Acid | |
| Males | ≥ 619.5 µmol/L |
| Females | ≥ 501.5 µmol/L |
| Bilirubin (total) | ≥ 34.2 µmol/L |
| Creatine Kinase (CK) | ≥ 3 x upper limit of normal |
| **Hematology** | |
| Hematocrit | |
| Males | ≤ 0.37 and decrease of ≥ 0.03 from Baseline |
| Females | ≤ 0.32 and decrease of ≥ 0.03 from Baseline |
| Hemoglobin | |
| Males | ≤ 115 g/L |
| Females | ≤ 95 g/L |
| White Blood Count (WBC) | ≤ 2.8 x $10^9$ /L or ≥ 16.0 x $10^9$ /L |
| Eosinophils | ≥ 10% |
| Neutrophils | Absolute Count < 1.5 x $10^9$ /L |
| Platelet Count | ≤ 100.0 x $10^9$ /L or ≥ 700.0 x $10^9$ /L |