# STATISTICAL ANALYSIS PLAN

## PROTOCOL D1052024

## A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, SINGLE ASCENDING DOSE (SAD) STUDY WITH LURASIDONE INJECTABLE SUSPENSION TO EVALUATE SAFETY, TOLERABILITY, AND PHARMACOKINETICS IN SUBJECTS WITH SCHIZOPHRENIA

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# STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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# 1. ABBREVIATIONS

| Abbreviation | Description |
|---|---|
| ACS | Abnormal, clinically significant |
| AE | Adverse event |
| Ae | Amount of drug excreted in urine |
| ALT | Alanine aminotransferase |
| ANCS | Abnormal, not clinically significant |
| AST | Aspartate aminotransferase |
| AUC | Area under the serum concentration-time curve |
| BLQ | Below Limit of Quantification |
| BMI | Body mass index |
| CI | Confidence interval |
| CL/F | Apparent clearance after extravascular administration |
| $C_{last}$ | The last postdose quantifiable serum concentration |
| CLR | Renal clearance |
| $C_{max}$ | Maximum observed serum concentration |
| CRF | Case report form (or electronic case report form) |
| C-SSRS | Columbia-suicide severity rating scale |
| CV | Coefficient of variation |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| fe | Fraction of drug excreted in urine |
| GCV | Geometric coefficient of variation |
| GM | Geometric mean |
| IPD | Important protocol deviation |
| ISF | Inform consent |
| ISAF | Injectable safety population |
| MedDRA | Medical dictionary for regulatory activities |
| OSAF | Oral safety population |
| MR | Metabolite to parent compound ratio |
| NCS | Not clinically significant |
| PANSS | Positive and Negative Syndrome Scale |
| PK | Pharmacokinetic |
| PD | Pharmacodynamic |
| PR | Time Between P Wave and QRS In Electrocardiography |
| PT | Preferred term |
| PTE | Pretreatment event |
| QRS | Electrocardiographic wave (complex or interval) |
| QTcF | QT interval with Fridericia's correction method |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Standard deviation |

| Abbreviation | Description |
|---|---|
| SOC | System organ class |
| SOP | Standard operating procedure |
| SRT | Safety review team |
| $t_{1/2}$ | Terminal half-life |
| $t_{last}$ | Time of the last postdose quantifiable serum concentration |
| $t_{max}$ | Time to reach $C_{max}$ |
| ULN | Upper limit of normal |
| ULQ | Upper limit of quantification |
| US | United states |
| $V_z/F$ | Apparent volume of distribution during the terminal phase after extravascular administration |
| WHODRUG | World Health Organization drug |
| $\lambda_z$ | Terminal rate constant |

# 2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of safety and pharmacokinetics (PK) data for Protocol D1052024. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version 1.0 dated 26 March 2018 and protocol amendment version 2.0, dated 13 June 2018.

# 3. STUDY OBJECTIVES

## 3.1. SAFETY OBJECTIVE

The safety objective is

To assess safety, tolerability, and pharmacokinetics (PK) of a single dose of lurasidone injectable suspension in subjects with schizophrenia.

## 3.2. PHARMACOKINETIC AND PHARMACODYNAMIC OBJECTIVES

Pharmacokinetic and Pharmacodynamic (PD) objectives are:

To assess the PK for the metabolites of lurasidone in serum (ID-14283, ID-14326, ID-11614, ID-20219 and ID-20220) and in urine (ID-14283, ID-14326, and ID-11614) after a single dose of lurasidone injectable suspension.

To assess Positive and Negative Syndrome Scale (PANSS) in subjects with schizophrenia after a single dose of lurasidone injectable suspension.

## 3.3. STUDY ENDPOINTS

### 3.3.1. SAFETY ENDPOINTS

Incidence of AEs, serious adverse events (SAEs), and AEs leading to study discontinuation

Incidence of injection site-related reactions, including injection site pain, injection site erythema, injection site induration, injection site ulcer, injection site granuloma and injection site swelling

Observed values and changes from baseline in clinical laboratory tests (hematology, serum chemistry, urinalysis, coagulation, and liver function), vital signs (respiratory rate, body temperature, supine blood pressure, and pulse), orthostatic effects (based on blood pressure and pulse rate), and 12-lead electrocardiograms (ECGs) parameters

Incidence and severity of subjects with suicidal ideation or suicidal behavior using the Columbia Suicide Severity Rating Scale (C-SSRS)

### 3.3.2. PHARMACOKINETIC ENDPOINTS

Pharmacokinetic parameters for lurasidone after Lurasidone injectable suspension administration

- Serum: $C_{max}$, $t_{max}$, $C_{last}$, $t_{last}$, $AUC_{0-144}$, $AUC_{0-last}$, $AUC_{0-inf}$, $\lambda_z$, $t_{1/2}$, CL/F, and $V_z$/F
- Urine: $Ae_{0-144h}$, $fe_{0-144}$, and $CL_R$

Pharmacokinetic parameters for metabolites after Lurasidone injectable suspension administration

- Serum: $C_{max}$, $t_{max}$, $C_{last}$, $t_{last}$, $AUC_{0-144}$, $AUC_{0-last}$, $AUC_{0-inf}$, $\lambda_z$, $t_{1/2}$, metabolite to parent ratio of $AUC_{0-inf}$ ($MR_{AUC0-inf}$), and $C_{max}$ ($MR_{Cmax}$) for ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220
- Urine: $Ae_{0-144h}$ for ID-14283, ID-14326, and ID-11614

### 3.3.3. PHARMACODYNAMIC ENDPOINT

Change from baseline, and placebo-corrected change from baseline in PANSS total score.

# 4. STUDY DESIGN

## 4.1. GENERAL DESCRIPTION

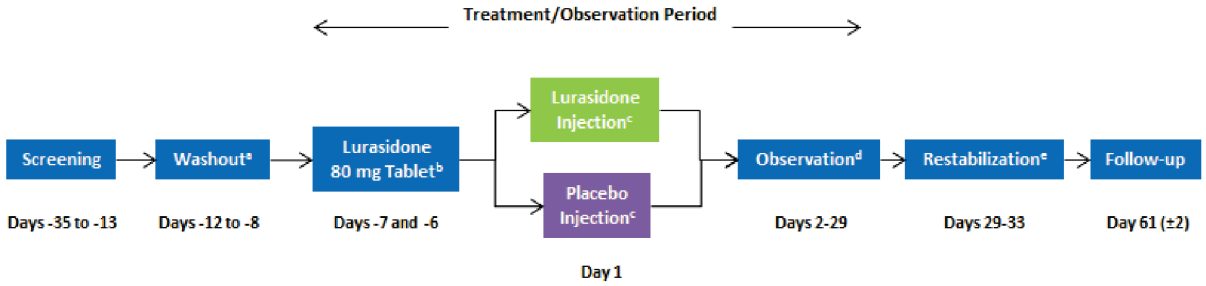
This is a single-center, randomized, double-blind, placebo-controlled, inpatient, single ascending dose (SAD) study designed to evaluate the safety, tolerability, and PK of lurasidone injectable suspension in subjects with schizophrenia. This study will determine the minimum intolerable dose (MID), the maximum tolerated dose (MTD) of lurasidone injectable suspension and characterize the PK profiles of lurasidone metabolites in serum (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) and urine (ID-14283, ID-14326, and ID-11614) in this subject population. The potential effects of gender on the PK of lurasidone injectable suspension and its metabolites will also be evaluated when applicable.

Subjects will receive oral lurasidone 80 mg tablets on Day -7 and Day -6 (one dose per day), and be monitored for 5 days to ensure the subject is able to tolerate lurasidone (ie, absence of moderate adverse events). Subjects who tolerate dosing with oral lurasidone 80 mg will be eligible for randomization to receive a single lurasidone injectable suspension or placebo injection on Day 1.

The study is planned to include up to 5 cohorts. A total of 8 subjects (6 active and 2 placebo) will be dosed in each cohort. Lurasidone injectable suspension dosing will be initiated at 30 mg given as an intramuscular (IM) injection. Subsequent cohorts are planned to be dosed at 75, 150, 300, and 450 mg IM. Dose strengths after the first dose level may be modified based on safety assessments and exposure to lurasidone injectable suspension.

All 5 planned dose cohorts may not be used, depending on the dose escalation strategy employed. Additional cohorts may be included in this study, as necessary, and determined following a review of safety and exposure of lurasidone injectable suspension. Planned dose levels may be modified or repeated based on the overall safety profile of the current and/or previous cohorts.

**Figure 1: Study Schematic**




[a] Eligible subjects must be washed out/tapered off of their current antipsychotic medications 5 to 6 half-lives prior to Day -8 (may begin as early as Day -19). Subjects are required to be inpatient from Day -12 to Day 15 (for treatment and observation) and Day 29 to Day 33 (for restabilization to previous medications). Subjects may remain inpatient up to Day 33 (at the Investigator's discretion).
[b] Subjects will receive 2 oral lurasidone 80 mg doses (Days -7 and -6) and be assessed for safety and tolerability for 5 days (Days -5 to -1) and to allow appropriate time to washout of the oral lurasidone dose.
[c] Randomization occurs on Day 1. Cohort 1 will receive a single lurasidone injectable suspension dose of 30 mg or a single placebo injection dose; thereafter, single lurasidone injectable suspension doses of 75, 150, 300, and 450 mg may be administered (cohorts 2-5).
[d] Subjects will be monitored for safety after the single lurasidone injectable suspension or placebo injection dose until Day 29. Subjects may be discharged on Day 15 at the Investigator's discretion.
[e] Subjects will restart prior medications (including antipsychotics) on Day 29 under observation of clinical site staff.

## 4.2. METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

The treatment schedule will be generated by a non-study biostatistician.

For each cohort, the randomization number will be sequentially assigned as subjects qualify for the study. Once 8 subjects per cohort are dosed, alternate subjects who are not needed to complete enrollment of a cohort will be discharged following reintroduction of their prior medication if they are clinically stable (in the Investigator's opinion).

Once a randomization number has been assigned, it cannot be reused.

Prior to dosing, all eligible subjects will be given a randomization number that assigns them to one of the two treatments. Randomization numbers will be assigned sequentially in the order the subject became eligible to participate in the study. The treatment schedule, a list consisting of the

randomization numbers and their corresponding treatment assignment will be generated according to appropriate standard operating procedure(s).

Subjects will receive single oral lurasidone 80 mg doses on Days -7 and -6 and be monitored for 5 days to ensure the subject is able to tolerate lurasidone (i.e., absence of moderate adverse events). Subjects who tolerate dosing with oral lurasidone 80 mg will be eligible for randomization on Day 1.

For Cohort 1, a sentinel group of 2 subjects will be dosed in a 1:1 ratio (lurasidone injection: placebo). A 7-day clinical assessment of safety and tolerability for the sentinel subjects will be made by the Investigator (including AEs, vital signs, and other clinically relevant findings), the remaining 6 subjects will be randomized in a 5:1 ratio (active: placebo). A sentinel group may not be required for future dose cohorts.

If less than 6 subjects in a cohort complete through Day 29, additional subjects will be enrolled and randomized in a 1:1 ratio (active: placebo) until at least 6 subjects have completed the cohort. If additional subjects need to be enrolled in a cohort, up to 6 additional randomization numbers will be provided in a 1:1 ratio.

## 4.3. BLINDING

All study drug injectable (active or placebo) will be dispensed according to the randomization schedule supplied by the Sponsor or its representative, using a method that will assure that subjects and blinded study site personnel remain blinded to the treatment (ie, active or placebo) being administered.

Provided doses will be clearly labelled with a unique subject identifier and verified during preparation and at the time of administration to mitigate any possibility of dosing/randomization error

During the conduct of the cohorts, in order to maintain the blind during the time of study drug administration, up until a safety review of AEs and other safety data for a cohort is conducted, an unblinded clinical site pharmacist/nurse will dispense study drug in a manner that will protect the blind upon administration

Subjects, Investigator staff, persons performing the assessments, clinical operations personnel, data analysts, and personnel at clinical laboratories will remain blind to the identity of the treatment from the time of randomization until database lock and unblinding, with the exception of the documented safety review process, using the following methods:

(1) randomization data are kept strictly confidential (eg, sealed envelopes kept in a locked filing cabinet or placed in a safe) until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions:

- bioanalytical lab personnel involved in the analysis of PK samples
- safety data review team members involved in regular review of safety data when it is determined that data need to be unblinded

(2) the identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, administration, and appearance;

(3) subjects will be dosed by an unblinded site staff member who is not part of the study team and will not conduct any other study related procedures. Preliminary PK concentration data transfer from the bioanalytical lab to the Sponsor's bioanalytical manager and from the Sponsor's bioanalytical manager to the PK scientist (for PK analysis) for each cohort safety review can only be handled with dummy IDs for study subjects. Final PK concentration data transfer can only be performed after the clinical database lock.

Treatment assignments for a particular cohort may be unblinded during a safety review meeting but only after a blinded review of the safety data has been completed.

Potentially unblinding laboratory results (prolactin) will be reviewed by an unblinded medical monitor and be blinded to the Subjects, site staff, and clinical team, as described in the study Medical Monitoring Plan. Results reaching pre-specified criteria will be provided to sponsor and SRT.

## 4.4. DETERMINATION OF SAMPLE SIZE

There will be no formal estimation for the sample size as no previous human PK data are available for lurasidone injectable suspension and the primary endpoints are safety. The sample size of 8 subjects per cohort (6 lurasidone injectable suspension subjects and 2 placebo subjects) is selected based on clinical and practical considerations for a study of this design.

Approximately 70 subjects are planned overall to ensure that up to 40 subjects receive lurasidone injectable suspension or placebo.

## 4.5. CHANGES IN THE CONDUCT OF THE STUDY

There is no change in the conduct of the study.

## 4.6. SCHEDULE OF EVENTS

Schedule of events can be found in Table 2 of the protocol.

## 4.7. CHANGES TO ANALYSIS FROM PROTOCOL

There were no changes in the analyses or definitions planned in the protocol.

# 5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Safety Review Team Analyses
- Final Analysis

## 5.1. SAFETY REVIEW TEAM (SRT)

After each cohort, a review of safety data (eg, AE [including potential psychotic symptoms and behavior], vital signs, laboratory data, standard 12-lead ECG, etc.) and lurasidone injectable suspension exposure data, including analyte concentrations and parameters, for all subjects (or at least 5 lurasidone and 1 placebo subjects completed) in each cohort will be performed. Subsequent dosing at the next dose level/cohort will not occur until safety and exposure data (from at least 14 days after the single lurasidone injectable suspension dose) have been evaluated by the Safety Review Team (SRT). The SRT consists of the PI, the Sponsor's Responsible Physician or designee, the Sponsor's Project Medical Lead, the Sponsor's Head of Translational Medicine and Early Development team or designee and the Medical Monitor. The SRT will also determine if sentinel subject dosing is required for study cohorts after Cohort 1.

The decision to proceed to the next dose level/cohort and at what dose level will also be made by the voting members of the SRT, based on a review of the clinical observations, laboratory data, and exposure data, and will require a majority agreement concerning acceptable safety and tolerability of lurasidone injectable suspension. Based on these safety reviews, a more conservative dose escalation may be used that will be less than the planned dose escalation, or subsequent cohorts may repeat a dose level or de-escalate. For each cohort, the SRT will monitor and review AE and exposure data 14 days and 28 days after the injection dose.

Treatment assignments for a particular cohort may be unblinded during a safety review meeting, but

only after a blinded review of the safety data has been completed. PK exposure data will be utilized in the safety review; thus, it will be necessary for the bioanalytical laboratory to be unblinded to treatment assignment for the subjects.

## 5.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this SAP, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment. (Update as required)

# 6. ANALYSIS POPULATIONS

Agreement and authorization of subjects included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

## 6.1. SAFETY [SAF] POPULATIONS

### 6.1.1. ORAL LURASIDONE SAFETY [OSAF] POPULATION

The Oral Lurasidone safety population (OSAF) will contain all subjects who signed the study specific informed consent and received at least one dose of Lurasidone oral tablet.

This population will be used for analysis of concomitant medications and adverse events data along with ISAF population.

### 6.1.2. INJECTABLE SAFETY [ISAF] POPULATION

The Injectable safety population (ISAF) will contain all subjects in the RND set who received injection of the double-blind study drug. Subjects will be classified according to treatment received.

This population will be used for analysis of baseline and safety data.

For summary tables in which data from both ISAF and OSAF populations are summarized, the term Safety Population will be used.

## 6.2. PHARMACOKINETIC POPULATION [PK]

The PK population will include all subjects in the ISAF Population who received lurasidone injectable suspension and have at least one post-dose quantifiable serum or urine lurasidone or metabolite(s) concentration, and had no important t protocol deviations or documented reason that a PK profile was unreliable. This population will be used for the analysis of PK data.

## 6.3. PHARMACODYNAMIC POPULATION [PD]

The PD population will include all subjects in the ISAF Population who have a valid baseline and at least one post baseline PANSS assessment. This population analysis will be used for the analysis of PD data.

# 7. GENERAL CONSIDERATIONS

## 7.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the injection study drug, (Day 1 is the day of the injection study drug) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

## 7.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to

reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

## 7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements collected prior to the first dose of study medication will contribute to the derivation of the baseline value.

Unscheduled measurements collected post baseline will not be included in by-visit summaries but will contribute to the EOS markedly abnormal post-baseline vital signs (MAPVS), markedly abnormal post-baseline laboratory value (MAPLV) and best/ worst case value where required (e.g. shift table).

Early termination (ET) data collected post baseline will be assigned to the next planned visit for that assessment. If the next scheduled visit is more than 14 days, then the ET data will not be included in the by-visit summary tables but will be included in the MAPVS, the MAPLV and the listings, This mapping will be done for all data points used in the PK and safety analyses.

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

## 7.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

Refer to appendix 1 for the visit convention for this study.

## 7.5. STATISTICAL TESTS

90% CIs will be used for the PK analysis.

## 7.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value
- For PK computations, the Percentage Coefficient of Variation (CV%), Geometric Mean (Geo Mean), and Percentage Geometric Coefficient of Variation (GCV% or 'Geometric CV%') will be computed as below:

$$CV\% = 100\ \frac{SD}{Mean}$$

$$Geo\ Mean = \ e^{Mean_{Log}}$$

$$GCV\% = (100)\sqrt{(e^{SD^2_{LOG}}) - 1}$$

Where SD is the sample standard deviation, Mean is the sample mean, $Mean_{Log}$ is the sample mean of the log transformed data, and $SD_{Log}$ is the sample standard deviation of the log transformed data. Note that when the data are lognormally distributed, CV% and GCV% are equal.

## 7.7. SOFTWARE VERSION

The PK analysis will be conducted using Phoenix® WinNonlin® Version 8.0, or higher (Certara L.P., Princeton, New Jersey). All other analyses will be conducted using SAS Version 9.4 or higher.

## 7.8. MISSING DATA

Missing PK data will be handled as described in Section 17 of this analysis plan.

## 7.9. EXAMINATION OF SUBGROUPS

Hemoglobin, hematocrit, uric acid, serum prolactin and QTcF will be presented by gender.

# 8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

# 9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.

The total number of screened subjects, the number of subjects who are screen failures, and the number of subjects randomized will be presented. The number and percentage of subjects who were randomly assigned to the double-blind injection period and the number of subjects in the Oral Lurasidone tablet period will be summarized. Subjects in the PK population will also be summarized. The number and percentage of subjects who complete and discontinue study will be summarized, along with reasons for study discontinuation. Subject disposition will be displayed by treatment (dose level of Lurasidone injectable suspension and pooled placebo) and overall.

Listing of subject disposition will also be provided.

Additionally, screen failure subjects will be presented in a data listing.

# 10. IMPORTANT PROTOCOL DEVIATIONS

Important Protocol Deviations (IPDs) will be identified and documented based on a review of potential IPDs. IPD's or events include any changes to the procedures that may impact the quality of the data or any circumstances that can alter the evaluation of the PK. The potential IPDs will be identified through programmatic checks of study data, as well as through review of selected data listings. The potential IPDs or events to be reviewed include, but are not limited to, subjects who:

- Did not meet inclusion/exclusion criteria.
- Did not meet continuation criteria.
- Received disallowed concomitant medication that is likely to impact the PK of lurasidone or its metabolites.

- Informed consent date obtained after date of first study procedure.
- Incomplete Injection dose administered
- Sample processing errors that lead to inaccurate bioanalytical results
- Incomplete PK profile collected

Additional IPDs may be identified from clinical review of Investigator comments or other data. Individual IPDs will be presented in a data listing.

Summary and listing of the IPD will be presented by treatment using ISAF population.

Additionally, listing of subject eligibility including inclusion and exclusion criteria will be presented in a listing.

# 11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Summary of demographic data and other baseline characteristics will be presented for the ISAF population. OSAF population will be used for the listing.

No statistical testing will be carried out for demographic or other baseline characteristics. Data will be summarized by treatment (dose level of Lurasidone injectable suspension and pooled placebo) and overall using descriptive statistics (number of subjects, mean, standard deviation (SD), median, minimum, and maximum) for continues variables, while categorical variables will be presented by number of subjects and percentage.

Additionally, data listing of demographic baseline characteristics will be presented

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of consent
- Sex
- Race
- Ethnicity
- Weight (kg)

- Height (cm) - calculated at screening
- BMI (kg/m$^2$) – calculated at screening
- Baseline PANSS Total Score

## 11.1. DERIVATIONS

- BMI (kg/ m$^2$) = weight (kg)/ [height (cm)/100]$^2$

# 12. MEDICAL HISTORY

Summary of medical history information will be presented for the ISAF population. OSAF population will be used for the listing.

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA v. 20.1 or higher).

- o Medical History conditions are defined as those conditions which stop prior to or at Screening.
- o Presented by SOC and PT.

The number and percentage of subject's medical history in each SOC and each PT will be summarized by treatment (dose level of Lurasidone injectable suspension and pooled placebo) and overall.

Data listing of medical history will also be provided.

# 13. PSYCHIATRIC HISTORY

Summary of psychiatric history information will be presented for the ISAF population. OSAF population will be used for the listing.

The number and percentage of subject's psychiatric history will be summarized by treatment (dose level of Lurasidone injectable suspension and pooled placebo) and overall.

Summary of psychiatric history will include number and percentage of schizophrenia subtype diagnosis, age at initial onset of schizophrenia, duration of schizophrenia from initial onset to

screening (years), number of prior hospitalizations for schizophrenia, and proportion of subjects with other psychiatric disorders present.

Duration of schizophrenia (years) = (Date of inform consent - date of schizophrenia onset)/365.25

Age at onset of schizophrenia (years) = date of schizophrenia onset – date of birth)/365.25

For subjects with partial onset dates of schizophrenia, impute the onset date using the following rules:

- If only day unknown, impute as the earlier of: last day of the month, or date of ICF.
- If both month and day unknown, impute as the earlier of: 31st December of the year, or date of ICF.

Data listing of psychiatric history will also be provided.

# 14. PRIOR AND CONCOMITANT MEDICATIONS

Summary of medications will be presented by oral and injectable treatment groups in the safety population. and coded using ATC (Anatomical Therapeutic Chemical) classification (i.e. ATC level 3) and preferred drug name according to the World Health Organization Drug (WHODRUG) version 2018 March 01 or more recent. ATC Level 2 will be used if ATC Level 3 is not available. OSAF population will be used for the listing.

Prior and Concomitant Medications for the oral Lurasidone tablet period:

- Prior Medication are all medications with the start date or an end date prior to the first dose of oral Lurasidone tablet period.
- Concomitant Medication are all medications with a start date or an end date on or after the date of the first dose of oral Lurasidone tablet period.

Concomitant Medications for the double-blind injection period is defined as:

- All medications with a start or an end date that is on or after the Day 1 of the double-blind injection period as well as those that were marked as “ongoing” during that period.

Concomitant Medications for both the oral Lurasidone tablet period and the double-blind injection period:

- A medication which begins prior to or during the Oral Lurasidone tablet period and continues into the double-blind Injection period will be considered a concomitant medication in both

periods. The same medication may be counted in both treatment periods for the same subject if it was taken during both periods.

The number and percentage of subjects using each prior medication will be summarized. Subjects with multiple uses of a medication will be counted only once for a given ATC class or preferred term.

The number and percentage of subjects using each concomitant medication will be summarized for the oral Lurasidone tablet period and for the double-blind injectable period by dose of Lurasidone injectable suspension and pooled placebo. Subjects with multiple uses of a medication will be counted only once for a given ATC class or preferred term.

Listing of prior and concomitant medications taken by subjects will also be provided.

# 15. STUDY DRUG EXPOSURE

Because this is a single dose study, study drug exposure will not be summarized as each randomized subject must have the same exposure.

# 16. STUDY DRUG COMPLIANCE

Because this is a single dose study, treatment compliance will not be summarized as each randomized subject must have the same compliance.

A data listing, by subject, containing the study drug dosing will be provided.

# 17. PHARMACOKINETIC ANALYSES

Blood samples for serum PK assessment will be collected at predose and 2 hours after tablet administration, and at predose and multiple timepoints up to 1440 (±48) hours after the injection dose. Urine samples for PK assessment will be collected at predose and up to 144 hours after the injection dose.

Analysis of the PK of lurasidone and metabolites (ID-14283, ID-14326, ID-11614, ID-20219 and ID-20220) in serum and urine will be the responsibility of the clinical pharmacokineticist at IQVIA. The PK summaries, data listings, figures, and the statistical analysis of the PK parameter and concentration data will be the responsibility of the biostatistician at IQVIA.

Subjects will be analyzed according to analyte and treatment received using actual time the sample

was collected. For SRT analyses, nominal times will be used for timing of the samples collected.

Pharmacokinetic variables (serum concentrations, urine amounts, and serum and urine PK parameters) will be summarized using descriptive statistics, including population size (N for sample size and n for available data), mean, SD, CV%, median, minimum, and maximum. For serum PK parameters, geometric mean (Geo mean), and GCV% will also be included, except for $t_{max}$, where only n, median, minimum, and maximum will be provided.

Source data (e.g., serum and urine concentrations) will be reported and analyzed to the same precision that it is received, regardless of how many significant figures or decimals the data carry, Derived data (e.g., urine amounts and parameters, serum PK parameters) will be rounded for reporting purposes both in the summary tables and by-subject listings. For the calculation of descriptive statistics and the statistical analysis, rounded values as presented in the data listings will be used. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g., $C_{max}$) will be reported and analyzed with the same precision as the source data.
- Parameters derived from actual elapsed sample collection times (e.g., $t_{max}$) will be reported in hours with 2 decimal places.
- Apparent terminal rate constant ($\lambda_z$) will be reported with 4 decimal places.

Reporting of mean (arithmetic and geometric), SD, minimum, median, and maximum will follow the rounding convention of the individual PK data and, in inferential analysis tables, associated CIs will be reported as percentages (%) to 2 decimal places. Coefficient of variation will always be reported to 1 decimal place.

Extra measurements (such as unscheduled or repeat assessments) will not be included in the descriptive statistics but will be included in subject listings. Pharmacokinetic summaries and inferential analyses (dose proportionality assessment) will be conducted for all subjects in the PK population. Data from subjects excluded from an analysis population will be included in the data listings, but not in the summaries or inferential analyses.

In general, serum (concentrations and parameters) and urine (amounts, fractions excreted, and parameters) PK data will be presented by analyte, dose level and subdivided by gender, as appropriate. Some minor modifications to the planned design of tables, figures, and listings may be necessary to accommodate data collected during the actual study conduct.

In the case of an important protocol deviation or event (see Section 10), affected PK data collected will be excluded from the summaries and statistical analyses, but will still be reported in the study

result listings.

# 17.1. SERUM AND URINE CONCENTRATION DATA

## 17.1.1. BLOOD SAMPLE FOR SERUM PK ASSESSMENT

Blood must be collected from all subjects at the time points indicated below.

| Day No. | Time Relative to Oral Lurasidone Dosing |
|---|---|
| -7 | Predose and 2 hours postdose |
| -6 | Predose and 2 hours postdose |
| **Day No.** | **Timepoint Relative to Lurasidone or Placebo Injection Dosing** |
| 1 | Predose and 2, 4, 6, and 12 hours postdose |
| 2 | 24 hours post-injection dose |
| 3 | 48 hours post-injection dose |
| 4 | 72 hours post-injection dose |
| 5 | 96 hours post-injection dose |
| 6 | 120 hours post-injection dose |
| 7 | 144 hours post-injection dose |
| 15 | 336 hours post-injection dose |
| 22 | 504 hours post-injection dose |
| 29 | 672 hours post-injection dose |
| 61 | 1440 hours post-injection dose |

## 17.1.2. URINE SAMPLE FOR PK ASSESSMENT

Urine samples will be collected from all subjects at the time points indicated below.

| Day No. | Time Interval Relative to Lurasidone or Placebo Injection Dosing |
|---|---|
| 1 | Predose -0.5 to 0 hour |
| 1/2 | 0 to 24 hours post-injection dose |
| 2/3 | 24 to 48 hours post-injection dose |
| 3/4 | 48 to 72 hours post-injection dose |
| 4/5 | 72 to 96 hours post-injection dose |

5/6 96 to 120 hours post-injection dose
6/7 120 to 144 hours post-injection dose.

### 17.1.3. SERUM AND URINE CONCENTRATION DATA ANALYSES

Listings of PK blood and urine sample collection times as well as derived sampling time deviations will be provided. Concentrations of lurasidone and metabolites in serum and urine will be listed and serum concentrations will be summarized by analyte, dose level, and time point.

Any serum or urine lurasidone and metabolite concentrations in listings and/or summary statistics which are below the limit of quantification will be represented as “BLQ" in listings and/or tables. If the calculated mean concentration is BLQ, the mean shall be reported as BLQ and the SD, CV%, geometric mean, and GCV% shall be reported as ND (not determined). Geometric mean and GCV% rules for BLQ only apply for reporting of $C_{max.}$ Minimum, median, and maximum may be reported and, if any are BLQ, they shall be reported as such and indicated as BLQ. Concentrations from serum and urine samples analyzed for the subset of subjects who receive placebo, if any, will be provided in a listing.

Graphical displays of individual subject and mean (+SD) serum lurasidone and metabolite concentrations will be presented on both linear and semi-logarithmic scales by time point including pre-dose.

## 17.2. PHARMACOKINETIC PARAMETERS

For the noncompartmental analysis of serum lurasidone and metabolite (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) concentration data, BLQ values will be considered 0 prior to $t_{max}$, missing between $t_{max}$ and $t_{last}$, and 0 after $t_{last}$. For PK parameter calculations, predose samples that are BLQ or missing will be assigned a numerical value of zero. Any quantifiable anomalous concentration values observed at predose will be identified in the study report and used for the computation of PK parameters. Any other BLQ concentrations will be assigned a value of zero if they precede quantifiable samples in the initial portion of the PK profile. A BLQ value that occurs between quantifiable data points, especially prior to $C_{max}$, will be evaluated to determine if an assigned concentration of zero makes sense, or if exclusion of the data is warranted. Following $C_{max}$, BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable concentration), it will be set to missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing, unless otherwise warranted by the concentration-time profile. Any concentration values observed at predose will be identified in the study report and used for the computation of AUC. A minimum of 3 postdose serum concentrations is

required for the calculation of serum PK parameters, except for $C_{max}$, $t_{max}$, and $MRC_{max}$ on Day -7 (only 1 postdose sample collection).

For the calculation of $AUC_{0-144}$, the concentration collected for the 144-hour timepoint and the actual sampling time will be used for calculating the partial area. Samples with time deviations at the 144-hour timepoint will be included for calculating $AUC_{0-144}$ and the descriptive and inferential statistics. Any subjects with a missing sample at the 144-hour timepoint will have $AUC_{0-144}$ excluded from the descriptive and inferential analyses.

$C_{max}$, $t_{max}$, $AUC_{0-last}$, and $AUC_{0-inf}$ for lurasidone injectable suspension will be the primary PK parameters and all others will be secondary PK parameters.

### 17.2.1. SERUM PARAMETERS AND DERIVATION

The following serum PK parameters will be estimated by noncompartmental methods for lurasidone and metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) using actual elapsed time from dosing on Day 1 following injectable suspension administration unless noted otherwise:

| | |
|---|---|
| $C_{max}$ | Maximum concentration in serum (ng/mL), obtained directly from the observed concentration versus time data (Day -7 and Day 1). |
| $t_{max}$ | Time of maximum concentration (h), obtained directly from the observed concentration versus time data (Day -7 and Day 1). |
| $C_{last}$ | The last postdose quantifiable serum concentration (ng/mL). |
| $t_{last}$ | Time of the last postdose quantifiable serum concentration (h). |
| $\lambda_z$ | Terminal rate constant (1/h), determined by linear regression of the terminal points of the log-linear concentration-time curve. Visual assessment will be used to identify the terminal linear phase of the concentration-time profile. |
| $t_{1/2}$ | Terminal half-life, calculated as $\ln(2)/\lambda_z$. |
| $AUC_{0-last}$ | Area under the concentration-time curve in serum from time zero (predose) to time of last quantifiable concentration (ng·h/mL), calculated by linear up log down trapezoidal summation. |
| $AUC_{0-inf}$ | Area under the concentration-time curve in serum from time zero (predose) extrapolated to infinite time (ng·h/mL), calculated by linear up log down trapezoidal summation and extrapolated to infinity by addition of the last quantifiable concentration divided by the terminal rate constant: $AUC_{0-last} + C_{last}/\lambda_z$. |

| | |
|---|---|
| $AUC_{0-144}$ | Area under the concentration-time curve in serum from time zero (predose) to 144 hours postdose (ng·h/mL), calculated by linear up log down trapezoidal summation (lurasidone only).<br>For the calculation of $AUC_{0-144}$, the concentration collected for the 144-hour timepoint and the actual sampling time will be used for calculating the partial area. |
| CL/F | Apparent systemic clearance (L/h) calculated as Dose/$AUC_{0-inf}$ (lurasidone only). |
| $V_z$/F | Apparent volume of distribution (L) calculated as Dose/$AUC_{0-inf}$/λz (lurasidone only). |
| $MRC_{max}$ | After oral dosing (Day -7 only), the ratio of metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) $C_{max}$ ($mC_{max}$) to parent (lurasidone HCl) $C_{max}$ ($pC_{max}$) calculated as: $mC_{max}$ divided by $pC_{max}$ (each ratio will be multiplied by 529.14 (MW of lurasidone HCl)/ 508.68, 508.68, 219.31, 305.37, or 321.37 (MW of ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220, respectively, to correct for the difference in molecular weight of the parent and the metabolites).<br>After injectable suspension dosing (Day 1), the ratio of metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) $C_{max}$ ($mC_{max}$) to parent (lurasidone injectable suspension) $C_{max}$ ($pC_{max}$) calculated as: $mC_{max}$ divided by $pC_{max}$ (each ratio will be multiplied by 492.68 (MW of lurasidone)/ 508.68, 508.68, 219.31, 305.37, or 321.37 (MW of ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220, respectively, to correct for the difference in molecular weight of the parent and the metabolites).<br>All metabolites will be expressed as free base after dosing. |
| $MRAUC_{0-inf}$ | The ratio of metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) $AUC_{0-inf}$ (mAUC) to parent (lurasidone injectable suspension) $AUC_{0-inf}$ (pAUC) calculated as: mAUC divided by pAUC (each ratio will be multiplied by 492.68 (MW of lurasidone)/ )/508.68, 508.68, 219.31, 305.37, or 321.37 (MW of ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220, respectively, to correct for the difference in molecular weight of the parent and the metabolites). |

The following serum PK parameters will be calculated for diagnostic purposes and listed only:

| | |
|---|---|
| t½, Interval | The time interval (h) of the log-linear regression to determine $\lambda_z$. |
| t½, N | Number of data points included in the log-linear regression analysis to determine $\lambda_z$. A minimum of 3 data points will be used for determination. |
| Rsq | Coefficient of determination (goodness-of-fit statistic for calculation of $\lambda_z$). If value is less than 0.800, then $t_{1/2}$, $\lambda_z$, $AUC_{0-inf}$, CL/F, and $V_z$/F will be listed but not included in summary presentations or statistical analyses |
| %AUCex | Percentage of $AUC_{0-inf}$ obtained by extrapolation, calculated as: |

[($C_{last}/\lambda_z$)/ $AUC_{0\text{-}inf}$ x 100]. If the extrapolated area ($C_{last}/\lambda_z$) is greater than 20% of $AUC_{0\text{-}inf}$, then $AUC_{0\text{-}inf}$, CL/F, and $V_z/F$ will be listed but not included in summary presentations or statistical analyses.

Scatter plots of individual and geometric mean values versus lurasidone dose will be presented for $C_{max}$, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ for lurasidone and metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220).

### 17.2.2. URINE PARAMETERS AND DERIVATION

$A_{et1\text{-}t2}$ Amount of lurasidone and metabolites (ID-14283, ID-14326, and ID-11614) (ng) excreted in urine from t1 to t2 where t1 to t2 = 0-24, 24-48, 48-72, 72-96, 96-120, and 120-144 hours, calculated as the product of urine volume and urine concentration determined for each interval. If the concentration is BLQ, the concentration will be set to 0.

Cum $A_{et1\text{-}t2}$ Cumulative amount of lurasidone and metabolites (ID-14283, ID-14326, and ID-11614) excreted in urine (ng) from t1 to t2 where t1 = 0 and t2 = 24, 48, 72, 96, 120, and 144 hours, calculated as the summation of $A_e$ for each collection interval. This will include the overall cumulative $A_e$ (ie, $A_{e,0\text{-}144}$).

$CL_R$ Renal clearance for lurasidone during the time interval 0 (predose) to 144 hours is calculated as:

$$CL_R = Ae_{0\text{-}144}/AUC_{0\text{-}144}$$

$f_e$ Percent of administered lurasidone excreted unchanged in urine during the time interval t1 to t2 where t1 to t2 = 0-24, 24-48, 48-72, 72-96, 96-120, and 120-144 hours, calculated as:

$$fe = (Ae_{t1\text{-}t2}/Dose)*100$$

Cum $f_{et1\text{-}t2}$ Cumulative percent of lurasidone excreted unchanged in urine during the time interval t1 to t2 where t1 = 0 and t2 = 24, 48, 72, 96, 120, and 144 hours calculated as the summation of $f_e$ for each collection interval. This will include the overall cumulative $f_e$ (i.e., $f_{e,0\text{-}144}$).

Graphical display of mean Cum Ae versus time, using the endpoint of the time interval, for lurasidone and metabolites (ID-14283, ID-14326, and ID-11614) will be presented by dose group and analyte.

All serum and urine PK parameter summaries will be presented by analyte, dose level, and subdivided by gender, as appropriate.

## 17.3. DOSE PROPORTIONALITY

Dose proportionality assessment for lurasidone and metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) for the administered dose range will be conducted using a power model for $C_{max}$, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$. The data will be fitted to a linear regression model:

$$\log(Y) = \alpha + \beta \log(X) + \varepsilon$$

where Y is the PK parameter, X is the dose, ε is the error term, and 'Log' represents the natural log. The estimate of the intercept and slope (β), together with its 90% CI, will be presented. Scatter plots of the natural log of $C_{max}$, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ versus log dose, along with the fitted regression line, will be presented. Dose proportionality will be assessed based on the inclusion of 1.0 in the CI for slope.

The adequacy of the model will be examined graphically. If the fit of the linear regression model does not seem adequate, then pairwise comparisons between dose groups for lurasidone will be made for $C_{max}$, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ using the following one way ANOVA model on dose normalized log-transformed PK parameters with fixed effect for dose group and employing CIs for the difference in mean between dose groups:

$$log\ \frac{Y_{ij}}{Dose_i} = \mu + Dose_i + \varepsilon_{ij}$$

where $Y_{ij}$ is the PK parameter [either $C_{max}$, $AUC_{0\text{-}last}$, or $AUC_{0\text{-}inf}$] value for the $i_{th}$ dose and $j_{th}$ subject in that dose group, $Dose_i$ is the $i_{th}$ dose group, and $\varepsilon_{ij}$ is the error term. No statistically significant difference between dose group means provides evidence of dose proportionality. From these analyses, for each PK analyte, least-squares (LS) mean for each dose group along with the corresponding 90% CI and LS mean for each pairwise dose group difference along the corresponding 90% CI in log-scale will be obtained. The results will be transformed back to the original scale by exponentiation to provide geometric LS mean for each dose group along with the associated 90% CI and geometric LS mean ratio along with the associated 90% CI for each pairwise ratio of dose groups.

Two additional models to assess dose proportionality will be completed in the same manner as stated above for the following dose ranges, 75 to 450 mg and 150 to 450 mg.

## 17.4. PHARMACODYNAMIC ANALYSIS

The PD variables of interest are change from baseline in PANSS total score.

If one PANSS item is missing, it will not be imputed. If one or more items are missing at a specific

visit, the total score will be set to missing at that visit.

### 17.4.1. EXPLORATORY PHARMACODYNAMIC VARIABLES & DERIVATIONS

The PANSS is an interview-based measure of the severity of psychopathology in adults with psychotic disorders. The measure is comprised of 30 items and 3 scales: The Positive subscale assesses hallucinations, delusions, and related symptoms; the Negative subscale assesses emotional withdrawal, lack of motivation, and similar symptoms; and the General Psychopathology subscale addresses other symptoms such as anxiety, somatic concern, and disorientation.

- The Positive subscales consist of the following items:
  1. Delusions
  2. Conceptual disorganization
  3. Hallucinatory Behavior
  4. Excitement
  5. Grandiosity
  6. Suspiciousness/persecution
  7. Hostility.
- The Negative subscales consist of the following items:
  1. Blunted Affect
  2. Emotional Withdrawal
  3. Poor Rapport
  4. Passive apathetic social Withdrawal
  5. Difficulty in abstract thinking
  6. Lack of spontaneity and flow of conversation
  7. Stereotyped thinking.

- The General Psychopathology subscale consists of the following items:

1. Somatic concerns
2. Anxiety
3. Guilt Feelings
4. Tension
5. Mannerism and posturing
6. Depression
7. Motor retardation
8. Uncooperativeness
9. Unusual thought content
10. Disorientation
11. Poor attention
12. Lack of judgment and insight
13. Disturbance of volition
14. Poor impulse control
15. Preoccupation
16. Active social avoidance

An anchored Likert scale from 1 to 7, where values of 2 and above indicate the presence of progressively more severe symptoms, is used to score each item. 30 Individual items are then summed to determine a total score.

Of the 30 items included in the PANSS, 7 constitute a Positive Scale, 7 a Negative Scale, and the remaining 16 a General Psychopathology Scale. The scores for these scales are arrived at by summation of ratings across component items. Therefore, the potential ranges are 7 to 49 for the Positive and Negative Scales, and 16 to 112 for the General Psychopathology Scale, where PANSS

total score ranges from 30-210.

### 17.4.2. Missing Data Method For the Pharmacodynamic Variable

The PANSS total score will be set to missing if any one item is missing.

### 17.4.3. Analysis of Pharmacodynamic Variables

The PD variable is change from baseline in PANSS total score.

Pharmacodynamic population will be used for the exploratory analysis.

Summary statistics (n, mean, SD, median, min, and max) for actual values and change from baseline in PANSS Total Score will be presented by visit and treatment (dose level of Lurasidone injectable suspension and pooled placebo).

Additionally, the PANSS score for each item, subscale scores and total score will also be listed.

## 18. Safety Outcomes

Adverse events and concomitant meds summary tables will be presented by oral and injectable treatment groups in the safety population. Injection site reaction related AEs will be presented by ISAF. All other safety summary data will be presented using ISAF population. OSAF population will be used for listings. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section. Summary tables will be presented by treatment (dose level of Lurasidone injectable suspension and pooled placebo).

AEs and all other safety data will be listed and summarized descriptively by treatment group (dose level of Lurasidone injectable suspension and pooled placebo) in tabular or graphical formats, as appropriate. Observed values, as well as change from baseline for clinical safety laboratories, vital signs, and ECGs will be listed and summarized descriptively in tabular formats, as appropriate. Any clinically significant results in clinical safety laboratories, vital signs, and ECGs will be listed and summarized. Frequency and severity of suicidality, based on the C-SSRS, will be listed and summarized.

## 18.1. Pretreatment Events and Adverse Events

Pretreatment events will be recorded from the time informed consent is provided at screening until the

time of first lurasidone oral tablet dose administration at Day-7.

Adverse events will be collected for each subject from immediately after the first lurasidone oral tablet dose administration at Day -7 until the follow-up visit at Day 61 (±2). Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 21.0 or higher.

- Adverse Events for the Oral Lurasidone tablet period is defined as an AE that started on or after the first dose of the oral lurasidone tablet.
- Adverse Events for the double-blind Injection period is defined as an AE that started on or after the date of the double-blind injection.
- Adverse Events that started on the Oral Lurasidone tablet period and continued the double-blind injection, but the severity did not change the AE will be reported in the Oral Lurasidone tablet period. If the severity of the AE gets worse, the AE will be considered in the double-blind injection period.

AEs will be summarized by treatment and by MedDRA system organ class (SOC) and Preferred Term (PT).

An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the SAP.

### 18.1.1. ALL AEs

AE tables will be summarized by oral Lurasidone tablet period and double-blind injection period (dose level of Lurasidone injectable suspension and pooled placebo).

AE tables will be summarized by oral Lurasidone tablet period and double-blind injection period (dose level of Lurasidone injectable suspension and pooled placebo).

Injection site reaction related AEs summary tables and figure will be presented by ISAF population.

Listing of all AEs will also be presented by OSAF population..

#### 18.1.1.1. Severity

- Severity for the oral Lurasidone tablet period is classed as mild/ moderate/ severe (increasing severity). AEs starting after the first Lurasidone tablet dose with a missing severity and ended during the double-blind injection period will be classified as severe

during that period. If a subject report an AE more than once within that SOC/ PT, the AE with the highest case severity will be used in the corresponding severity summaries.

- Severity for the double-blind injection period is classed as mild/ moderate/ severe (increasing severity). AEs starting after the first Lurasidone injection dose with a missing severity will be classified as severe. If a subject report an AE more than once within that SOC/ PT, the AE with the highest case severity will be used in the corresponding severity summaries.

#### 18.1.1.2. Relationship to Study Treatment

Relationship, as indicated by the Investigator, is classed as “not related”, “possible”, “probable (increasing severity of relationship) or definite.

For summaries by relationship to the study drug, AEs will be grouped as “related” or “not related.”.”

- AE Related: AEs with relationship to study drug assessed as “possible,” “probable,” or “definite”
- AE not Related: AEs with relationship to study drug assessed as “not related”
- AEs with a missing relationship to study drug will be regarded as “related”

If a subject report the same AE more than once within that SOC/ PT, the AE with the strongest case relationship to study drug will be used in the corresponding relationship summaries.

### 18.1.2. AEs Leading to Discontinuation of Study

AEs leading to discontinuation of the study will be identified by using the AE page of the electronic case report form (eCRF), where “Caused Study Discontinuation” is answered as “Yes”.

Summary and Listing of AEs leading to discontinuation of the study, will be presented.

### 18.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as “Serious” on the Adverse Events page of the (e)CRF.

Summaries of SAEs will be provided.

Listing of SAEs will also be presented.

### 18.1.4. ADVERSE EVENTS LEADING TO DEATH

AEs leading to death are those events which are recorded with an AE outcome of "Fatal" on the Adverse Events page of the (e)CRF.

### 18.1.5. DURATION OF INJECTION SITE REACTION AEs FOR THE DOUBLE-BLIND INJECTION PERIOD

The duration of the injection site reaction AEs is calculated as the AE end date minus the AE start date during the period from start of double-blind injection period (day 1) through follow-up visit date (day 61 +2). If the end date of the AE is missing, then the duration of the AE will be imputed using the last contact date for subjects who withdrew from the study, or the study completion date for subjects who completed the study. For subjects experiencing more than one occurrence of an AE, only the duration of the longest event will be summarized.

ISAF population will be used for the duration of AEs. The time (in days) to first AE in the double-blind Injection period and the duration (in days) of the AEs will be presented in tabular and figure format summarized by Lurasidone injection dose groups, all Lurasidone dose groups and pooled placebo. The following will be presented for the duration of AEs.

- Figure of the incidence of any post-injection AE by study day.
- Duration of all injection site reaction related AEs in Days by Treatment

## 18.2. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for clinical chemistry, hematology, and urinalysis Lipid Panel, Thyroid Panel, Coagulation Panel Urine Drug Screening, Serology Panel, and Other Tests.

A list of laboratory assessments to be included in the outputs is included in appendix II/ the protocol, Section 21.

ISAF population will be used for all laboratory summaries. OSAF population will be used for the listings.

Presentations will use standard international (SI) Units

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Note that handling of retests and unscheduled measurements are included in Section 7.3 to save repetition in different sections of the SAP

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements) and by treatment.
- Shift from baseline by treatment and visit of subject with laboratory values below, within, and above the normal range.
- Incidence of subjects with a Markedly Abnormal Post-Baseline Laboratory value (MAPLV) for select parameters by treatment.
- Actual and change from baseline for selected serum chemistry parameters (Hemoglobin, Haematocrit, Uric Acid and serum prolactin) values by visit, treatment and by gender.
- Shift from baseline by visit, treatment and by gender of subject for selected serum chemistry parameters (Hemoglobin, Haematocrit, Uric Acid and serum prolactin) below, within, and above the normal range.
- Incidence of subjects with a Markedly Abnormal Post-Baseline Laboratory value (MAPLV) for selected serum chemistry parameters (Hemoglobin, Haematocrit, Uric Acid and serum prolactin) values by treatment and by gender.
- Data listings for all laboratory parameters along with comments will be provided. Results outside of the reference range will be flagged.

### 18.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).

- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal quantitative safety (and other) laboratory assessments will also be identified in accordance with the predefined markedly abnormal criteria as presented in Appendix 3.

## 18.3. ECG EVALUATIONS

Results from the central ECG (Electrocardiogram) Reading Centre will be included in the reporting of this study. Safety population will be used.

ISAF population will be used for all ECG summaries. OSAF population will be used for the listings.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QTcF Interval (msec)
- QTcB Interval (msec)
- QT Interval (msec)
- HR (bpm)
- Overall assessment of ECG (Investigator's judgment):

o Normal
o Abnormal, Not Clinically Significant (ANCS)
o Abnormal, Clinically Significant (ACS)

The following summaries and listings will be provided for ECG data:

- Observed values and changes from baseline will be presented at each evaluation timepoint and by treatment. Data will be summarized using descriptive statistics (n, mean, mean, median, minimum, maximum)

Summary of ECG categories of Markedly Abnormal Criteria will be summarized by timepoint and by

treatment in frequency tables with counts and percentages for number of subjects. This will include overall for the oral period and double-blind injection period. The overall oral period includes Day -7, Day -6, Day 1 (Predose) and Baseline and all unscheduled visits within this period. The overall double-blind (DB) injection period includes Day 1 (postdose timepoints) to Day 61 and all unscheduled visits within this period.

- Listing of Electrocardiogram clinical interpretation of ECG findings including Markedly Abnormal Criteria

### 18.3.1. ECG MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined markedly abnormal criteria

- Absolute values for QTcF and QTcB will be classified as:

o Males: > 450 msec or Females: > 470 msec
o > 450 msec
o > 480 msec
o > 500 msec

- Change from Baseline for QTcF and QTcB will be classified as:

o > 30 msec increase from baseline
o > 60 msec increase from baseline

- Change from Baseline for PR interval will be classified as:
  - increase in PR interval from baseline > 25% and a PR interval > 200 msec;
- Change from Baseline for QRS interval will be classified as:
  - increase in QRS interval from baseline > 25% and a QRS interval > 120 msec;
- Change from Baseline for HR will be classified as:
  - decrease in HR from baseline > 25% and a HR < 50 bpm;
  - and increase in HR from baseline > 25% and a HR > 100 bpm

## 18.4. VITAL SIGNS

Vital signs baseline is defined as the pre-injection dose assessment.

ISAF will be used for all vital signs summaries. OSAF will be used for the listings,

The following Vital Signs measurements will be reported for this study:

- [Standing/ Supine] Systolic Blood Pressure (mmHg)
- [Standing/ Supine] Diastolic Blood Pressure (mmHg)
- [Standing/ Supine] Pulse Rate (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature ($^0$C)
- Weight (kg)
- BMI (kg/m$^2$)

The following summaries will be provided for vital signs data:

- Observed values and changes from baseline will be presented at each evaluation timepoint and by treatment. Data will be summarized using descriptive statistics (n, mean, mean, median, minimum, maximum)
- Incidence of markedly abnormal post-baseline vital sign values (MAPVS) will be presented by treatment
- Listing of Vital Signs.
- Data listing of Markedly Abnormal Post-Baseline Vital Sign Values (MAPVS).

### 18.4.1. ORTHOSTATIC HYPOTENSION

Orthostatic hypotension is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure upon standing, compared to the systolic and diastolic blood pressures measured in the supine position, respectively.

Orthostatic tachycardia is defined as a pulse rate increase of at least 20 bpm and a pulse rate > 100 bpm upon standing, compared to the pulse rate measured in the supine position.

ISAF population will be used for all summaries. OSAF will be used for the listings.

Summary of Subjects with Orthostatic Hypotension, Orthostatic Tachycardia and any Orthostatic hypotension or Orthostatic Tachycardia will be provided. Data will be presented by treatment.

### 18.4.2. MARKEDLY ABNORMAL CRITERIA VITAL SIGNS (MAPVS)

Markedly abnormal post-baseline Vital Signs (MAPVS) will be identified in accordance with the following predefined markedly abnormal criteria

| Variable (unit) | Low | High |
|---|---|---|
| SBP (mmHg) | ≤ 90 mmHg AND<br>change from baseline ≤ -20 mmHg | ≥ 180 mmHg AND<br>change from baseline ≥ 20 mmHg |
| DBP (mmHg) | ≤ 50 mmHg AND<br>change from baseline ≤ -15 mmHg | ≥ 105 mmHg AND<br>change from baseline ≥ 15 mmHg |
| Respiratory rate (breaths/ minute) | ≤ 10 breaths/minute AND<br>Percentage change from baseline ≤ - 50% breaths/minute | ≥ 25 breaths/minute AND<br>Parentage change from baseline ≥ 50% breaths/ minute |
| Pulse rate (bpm) | ≤ 50 bpm AND<br>change from baseline ≤ -15 bpm | ≥ 120 bpm AND<br>change from baseline ≥ 15 bpm |
| Body temperature (c) | NA | ≥ 38.3 ˚C |
| Weight (kg) | percentage change from baseline ≤ - 7.0 % | percentage change from baseline ≥ 7.0 % |

## 18.5. PHYSICAL EXAMINATION

The clinically significant abnormalities or changes which are noted in the physical exams are recorded as part of medical history (if noted during screening) and as adverse events at other timepoints. Their summaries/listings are thus included in the medical history and adverse events outputs.

A listing displaying whether a physical examination was performed for each subject and the date of the physical examination. OSAF population will be used.

# 18.6. OTHER SAFETY ASSESSMENTS

## 18.6.1. INVESTIGATOR INJECTION SITE ASSESSMENTS

The Investigator will assess the injection site using a rating of Grade 1-4 on each of the 4 items (pain, tenderness, erythema/redness, and induration/swelling).

ISAF population will be used for all investigator injection site reaction summaries.

Injection site reactions will be assessed for severity according to each of the following categories (per the Investigator's judgement):

| Local Reaction to Injectable Product | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) | Potentially Life Threatening (Grade 4) |
|---|---|---|---|---|
| Pain | Does not interfere with activity | Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity | Any use of narcotic pain reliever or prevents daily activity | Emergency room (ER) visit or hospitalization |
| Tenderness | Mild discomfort to touch | Discomfort with movement | Significant discomfort at rest | ER visit or hospitalization |
| Erythema/Redness | 2.5 – 5 cm | 5.1 – 10 cm | > 10 cm | Necrosis or exfoliative dermatitis |
| Induration/Swelling | 2.5 – 5 cm and does not interfere with activity | 5.1 – 10 cm or interferes with activity | > 10 cm or prevents daily activity | Necrosis |

The following summaries will be provided for investigator injection site assessment data.

- Proportion of subjects with mild, moderate, severe, life-threatening, and any severity of each of the four injection site reaction assessments by treatment and scheduled timepoint.
- Data listing of investigator injection site assessment.

### 18.6.2. SUBJECT INJECTION SITE PAIN SCORE

The subject will assess their injection site pain using a rating of 0-10 on a Likert scale (0 = no pain, 10 = worst pain). This will be completed prior to the Investigator's injection site assessment.

ISAF population will be used for all subject injection site pain score summaries.

Subject injection site pain score will be categorized as follows:

- 0 = No pain
- 1-3 = Mild pain
- 4-6 = Moderate pain
- 7-10 = Severe pain

The following summaries will be provided for subject injection site pain score data.

- Descriptive Statistics for the pain score (0-10) by treatment and scheduled timepoint.
- Frequency and percentage of the pain score categories (no pain, mild pain, moderate pain and severe pain) by treatment and scheduled timepoint.
- Data listing of subject injection site pain score.

### 18.6.3. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

The C SSRS is a tool designed to systematically assess and track suicidal AEs (suicidal behavior and suicidal ideation) throughout the study. The strength of this suicide classification system is in its ability to comprehensively identify suicidal events while limiting the over-identification of suicidal behavior

This study utilizes 2 versions of the C-SSRS, the Screening/Baseline version and at the Since Last Visit version. The Screening/Baseline version consists of "Lifetime" Questionnaire and "Past 1 Month" Questionnaire, where Since Last Visit version consists of "Lifetime" Questionnaire.

Screening Baseline version will be administered at Screening Visit, where Since Last Visit version will be administered at the subsequent visits.

Summary of C-SSRS will be presented for the ISAF population. OSAF population will be used for the listing.

### 18.6.3.1. C-SSRS Variables & Derivations

The following outcomes are C-SSRS categories have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the C-SSRS endpoints, and to provide clarity in the presentation of the results.

C-SSRS consists of the following categories:

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

The categories of the C-SSRS are not mutually exclusive. Subjects will be counted in each category for which they have an event.

C-SSRS Composite Endpoints

- The following composite endpoints for the C-SSRS will be derived as follows.
- Suicidal Ideation: A “yes” answer at any time during treatment to any one of the five suicidal ideation questions (categories 1-5) on the C-SSRS.

- Suicidal Behavior: A “yes” answer at any time during treatment to any one of the five suicidal behavior questions (categories 6-10) on the C-SSRS.

- Suicidal Ideation or Suicidal Behavior: A “yes” answer at any time during treatment to any one of the ten-suicidal ideation and behavior questions (categories 1-10) on the C-SSRS.

- Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response.

#### 18.6.3.2. Analyses of C-SSRS Variables

The number and percentage of subjects with an event in each of the 10 categories, composite endpoint, or with non-suicidal self-injurious behavior at screening visit will be presented using Screening/Baseline version for the “Lifetime” questionnaire and the “Past 1 Month” questionnaire. For all subsequent visits where C-SSRS is administered “Since Last Visit” version will be used. The percentage will be presented by treatment.

Safety population will be used for all C-SSRS summaries and listings.

The following comparative endpoints will also be presented (n/m %), where “Treatment emergence” is used for outcomes that include events that first emerge or worsen and “Emergence” is used for outcomes that include events that first emerge.

- Treatment-emergent suicidal ideation compared to recent history: An increase in the maximum suicidal ideation score during treatment from the maximum suicidal ideation category at Baseline (C-SSRS scales taken during the specified pre-treatment period; excludes “lifetime” scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).

- Treatment-emergent serious suicidal ideation compared to recent history: An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment from not having serious suicidal ideation (scores of 0-3) at Baseline (C-SSRS scales taken during the specified pretreatment period; excludes “lifetime” scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).

- Emergence of serious suicidal ideation compared to recent history: An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment from no suicidal ideation (scores of 0) at Baseline (CSSRS scales taken during the specified pre-treatment period; excludes “lifetime” scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale).

- Improvement in suicidal ideation at a time point of interest compared to Baseline: An improvement in this endpoint can be considered as a decrease in suicidal ideation score at the time point of interest (e.g., the last measurement during treatment) from the baseline measurement (e.g., the measurement taken just prior to treatment). This analysis should only be performed for studies in which a baseline C-SSRS can be defined (i.e., having improvement from the worse event over a lifetime is not clinically meaningful).

- Emergence of suicidal behavior compared to all prior history: The occurrence of suicidal behavior (categories 6-10) during treatment from not having suicidal behavior (categories 6-10) prior to treatment (includes “lifetime” and/or “screening” scores from the Baseline C-SSRS scale, Screening C-SSRS scale, or Baseline/Screening C-SSRS scale, and any “Since Last Visit” from the Since Last Visit C-SSRS scales taken prior to treatment).

Note that missing data should not be imputed.

The following summaries will be provided for the C-SSRS data:

- The number and percentage of subjects with each type of suicidal ideation and suicidal behavior will be summarized by treatment
- The number and percentage of subjects with treatment emergent suicidal ideation, serious suicidal ideation, and suicidal behavior will be summarized by treatment
- Responses to each of the questions on the C-SSRS will be listed

# 19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments
- These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

# 20. REFERENCES

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**Base SAS® 9.2 Procedures Guide**. Copyright © 2009 by SAS Institute Inc., Cary, NC, USA.

# APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

## DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

## PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

| Treatment Group | For Tables, Listings and Graphs |
|---|---|
| Oral Lurasidone 80mg | Oral Lurasidone 80mg |
| Inj. Lurasidone 30mg | Inj. Lurasidone 30mg |
| Inj. Lurasidone 75mg | Inj. Lurasidone 75mg |
| Inj. Lurasidone 150mg | Inj. Lurasidone 150mg |
| Inj. Lurasidone 300mg | Inj. Lurasidone 300mg |
| Inj. Lurasidone 450mg | Inj. Lurasidone 450mg |
| Inj. Placebo | Inj. Placebo |

# APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

## ALGORITHM FOR ADVERSE EVENTS:

### ORAL LURASIDONE TABLET PERIOD

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If start date < oral tablet start date, then not AE<br>If start date >= oral tablet start date and before injection start date, then AE |
| | Partial | If start date < oral tablet start date, then not AE<br>If start date >= oral tablet start date, and before injection start date then AE |
| | Missing | If start date < oral tablet start date, then not AE<br>If start date >= oral tablet start date and before injection start date, then AE |
| | | |
| Partial, but known components show that it cannot be on or after oral tablet start date | Known | Pre-treatment events |
| | Partial | Pre-treatment events |
| | Missing | Pre-treatment events |
| | | |
| Partial, could be on or after oral tablet start date and before injection start date, | Known | If stop date < oral tablet start date, then Pre-treatment events<br>If stop date >= oral tablet start date and before injection start date, then AE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < oral tablet start date, then Pre-treatment events<br>If stop date >= oral tablet start date and before injection start date, then AE |
| | Missing | Assumed AE |
| | | |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Missing | Known | If stop date < oral tablet start date, then Pre-treatment events<br>If stop date >= oral tablet start date and before injection start date, then AE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < oral tablet start date and before injection start date, then not AE<br>If stop date >= oral tablet start date and before injection start date, then AE |
| | Missing | Assumed AE |

## DOUBLE-BLIND INJECTION PERIOD

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If start date < injection start date and after oral tablet, then not AE<br>If start date >= injection start date, then AE |
| | Partial | If start date < injection start date and after oral tablet, then not AE<br>If start date >= injection start date and after oral tablet, then AE |
| | Missing | If start date < injection start date and after oral tablet, then not AE<br>If start date >= injection start date and after oral tablet, then AE |
| | | |
| Partial, could be on or after injection start date | Known | If stop date >= injection start date, then AE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date >= injection start date, then AE |
| | Missing | Assumed AE |
| | | |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Missing | Known | If stop date >= injection start date, then AE |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If stop date < injection start date, then not AE<br>If stop date >= injection start date, then AE |
| | Missing | Assumed AE |

## ALGORITHM FOR PRIOR / CONCOMITANT:

### ORAL LURASIDONE TABLET PERIOD

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If stop date < oral tablet start date, assign as prior<br><br>If both start date and stop date >= oral tablet start date, assign as concomitant<br><br>If stop date >= oral tablet start date and start date < oral tablet start date, assign as both prior and concomitant |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date < oral tablet start date, assign as prior<br><br>If both start date and stop date >= oral tablet start date, assign as concomitant<br><br>If stop date >= oral tablet start date and start date < oral tablet start date, assign as both prior and concomitant |
| | Missing | If stop date is missing then |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| | | If start date >= oral tablet start date, assign as concomitant<br><br>If start date < oral tablet start date, assign as both prior and concomitant |
| | | |
| Partial | Known | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br><br>If stop date < oral tablet start date, assign as prior<br><br>If both start date and stop date >= oral tablet start date, assign as concomitant<br><br>If stop date >= oral tablet start date and start date < oral tablet start date, assign as both prior and concomitant |
| | Partial | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown)<br><br>Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown) , then:<br><br>If stop date < oral tablet start date, assign as prior<br><br>If both start date and stop date >= oral tablet start date, assign as concomitant<br><br>If stop date >= oral tablet start date and start date < oral tablet start date, assign as both prior and concomitant |
| | Missing | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br><br>If start date >= oral tablet start date, assign as concomitant |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| | | If start date < oral tablet start date, assign as both prior and concomitant |
| | | |
| Missing | Known | If stop date < oral tablet start date, assign as prior<br><br>If stop date >= oral tablet start date, assign as both prior and concomitant |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date < oral tablet start date, assign as prior<br><br>If stop date >= oral tablet start date, assign as both prior and concomitant |
| | Missing | Assign as both prior and concomitant |

## DOUBLE-BLIND INJECTION PERIOD

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If stop date >= injection date, assign as concomitant |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date >= injection date, assign as concomitant |
| | Missing | If the subject is in ISAF population and start date <= end of study/early termination, assign as concomitant |
| | | |
| Partial | Known | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| | | If stop date >= injection date, assign as concomitant |
| | Partial | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown)<br><br>Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date >= injection date, assign as concomitant |
| | Missing | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br><br>If start date <= end of study/early termination, assign as concomitant |
| | | |
| Missing | Known | If stop date >= injection date, assign as concomitant |
| | Partial | If stop date >= injection date, assign as concomitant |
| | Missing | Assign as concomitant |

## PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order: Hours will be presented as appropriate based on the measurements.

| Visit | Timepoint |
|---|---|
| Screening | Screening |
| Day -12 | Day -12 |
| Day -8 | Day -8 |
| Time Relative to Oral Lurasidone Dosing | |
| Day -7 | Predose |
| | 2 hours postdose |
| Day -6 | Predose |

| Visit | Timepoint |
|---|---|
| | 2 hours postdose |
| Relative to Lurasidone or Placebo Injection Dosing | |
| Day 1 | Day1 (Predose) |
| | 2 hours postdose |
| | 4 hours postdose |
| | 6 hours postdose |
| | 12 hours postdose |
| Baseline | Baseline |
| Day 2 | 24 hours post-injection dose |
| Day 3 | 48 hours post-injection dose |
| Day 4 | 72 hours post-injection dose |
| Day 5 | 96 hours post-injection dose |
| Day 6 | 120 hours post-injection dose |
| Day 7 | 144 hours post-injection dose |
| Day 15 | 336 hours post-injection dose |
| Day 22 | 504 hours post-injection dose |
| Day 29 | 672 hours post-injection dose |
| Day 61 (Follow-Up) | 1440 hours post-injection dose |

## LISTINGS

All listings will be ordered by the following:

- Cohort
- Dose Level
- Subject ID
- Date/time (where applicable) - listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first,

# APPENDIX 3. PREDEFINED MARKEDLY ABNORMAL CRITERIA

## STANDARD ADULT MARKEDLY ABNORMAL POST-BASELINE LABORATORY VALUE (MAPLV) PARAMETERS – SI UNITS

| Category<br>Parameter Name<br>Age/Gender Restriction, if any | Low | High |
|---|---|---|
| HEMATOLOGY | | |
| WBC | ≤ 2.8 x $10^9$/L | ≥ 16 x $10^9$/L |
| Neutrophils (abs) | < 0.5 x $10^9$/L | > 13.5 x $10^9$/L |
| Lymphocytes (abs) | N/A | > 12 x $10^9$/L |
| Monocytes (abs) | N/A | > 2.5 x $10^9$/L |
| Eosinophils (abs) | N/A | > 1.6 x $10^9$/L |
| Basophils (abs) | N/A | > 1.6 x $10^9$/L |
| Neutrophils (relative) | ≤ 0.15 | > 0.85 |
| Lymphocytes (relative) | N/A | ≥ 0.75 |
| Monocytes (relative) | N/A | ≥ 0.15 |
| Eosinophils (relative) | N/A | ≥ 0.10 |
| Basophils (relative) | N/A | ≥ 0.10 |
| Hemoglobin<br>Male<br>Female | <br>≤ 115 g/L<br>≤ 95 g/L | <br>≥ 190 g/L<br>≥ 175 g/L |
| Hematocrit<br>Male<br>Female | <br>≤ 0.37<br>≤ 0.32 | <br>≥ 0.60<br>≥ 0.54 |
| RBC | ≤ 3.5 x $10^{12}$/L | ≥ 6.4 x $10^{12}$/L |
| Platelet Count | ≤ 75 x $10^9$/L | ≥ 700 x $10^9$/L |
| SERUM CHEMISTRY | | |
| Sodium | < 130 mmol/L | > 150 mmol/L |
| Potassium | < 3 mmol/L | > 5.5 mmol/L |
| Chloride | ≤ 90 mmol/L | ≥ 118 mmol/L |
| Calcium | < 1.75 mmol/L | ≥ 3.1 mmol/L |
| Phosphate | < 0.65 mmol/L | > 1.65 mmol/L |

| Category<br>Parameter Name<br>Age/Gender Restriction, if any | Low | High |
|---|---|---|
| AST （IU/L） | N/A | ≥ 3 x ULN |
| ALT （IU/L） | N/A | ≥ 3 x ULN |
| Alkaline Phosphatase (IU/L） | N/A | ≥ 1.5 x ULN |
| Creatinine | N/A | ≥ 177 umol/L |
| BUN | N/A | ≥ 10.7 mmol/L |
| Total bilirubin (mg/dL) | N/A | ≥ 34.2 umol/L OR > 2 x ULN |
| Total protein | ≤ 45 g/L | ≥ 100 g/L |
| Albumin | ≤ 25 g/L | N/A |
| Total-Cholesterol (fasting) | N/A | > 7.76 mmol/L |
| HDL-Cholesterol (fasting) | < 0.78 mmol/L | N/A |
| LDL-Cholesterol (fasting) | N/A | > 4.14 mmol/L |
| Triglycerides | N/A | > 3.42 mmol/L |
| Uric acid<br>Male<br>Female | <br>N/A<br>N/A | <br>> 595 umol/L<br>> 476 umol/L |
| Glucose (Fasting) | < 2.78 mmol/L | > 13.9 mmol/L |
| Prolactin | NA | Female: >= 146.0 ng/mL<br>Male: >= 88.5 ng/mL |
| COAGULATION | | |
| aPTT (sec) | N/A | > 1.5 ULN |
| INR (ratio) | N/A | > 1.5 ULN |
| THYROID FUNCTION | | |
| Free T3 | < 3.07 pmol/L | > 6.38 pmol/L |
| Free T4 | < 9.65 pmol/L | > 22.5 pmol/L |

# APPENDIX 4. LIST OF TABLES, FIGURES, AND LISTINGS

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|---|---|
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