Lurasidone Injectable Suspension
DSP-1349M
Clinical Study Protocol D1052024

A Randomized, Double Blind, Placebo Controlled, Single Ascending Dose Study with Lurasidone Injectable Suspension to Evaluate Safety, Tolerability, and Pharmacokinetics in Subjects with Schizophrenia

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EMERGENCY CONTACTS

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Responsible Physician	Sunovion Pharmaceuticals Inc.	Telephone: Email:
Medical Advisor	IQVIA	Telephone: Email:
24-Hour Serious Adverse Event/Pregnancy Reporting in the United States	PPD Pharmacovigilance (PVG)	Hotline Number: Email: United States Fax: Outside United States Fax:

1. SYNOPSIS

Name of Sponsor: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: Lurasidone injectable suspension

Name of Active Ingredient: Lurasidone (DSP-1349M)

Proposed Indication: Schizophrenia

Title of Study: A Randomized, Double Blind, Placebo Controlled, Single Ascending Dose Study with Lurasidone Injectable Suspension to Evaluate Safety, Tolerability, and Pharmacokinetics in Subjects with Schizophrenia

Study Centers: 1 site in the United States

Study Objectives:

Safety Objective

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

Pharmacokinetic and Pharmacodynamic Objectives

- 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.

Study Design

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 and its 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.

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 at the ventrogluteal site. Subsequent cohorts are planned to be dosed at 75, 150, 300, and 450 mg IM at the ventrogluteal site. 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.

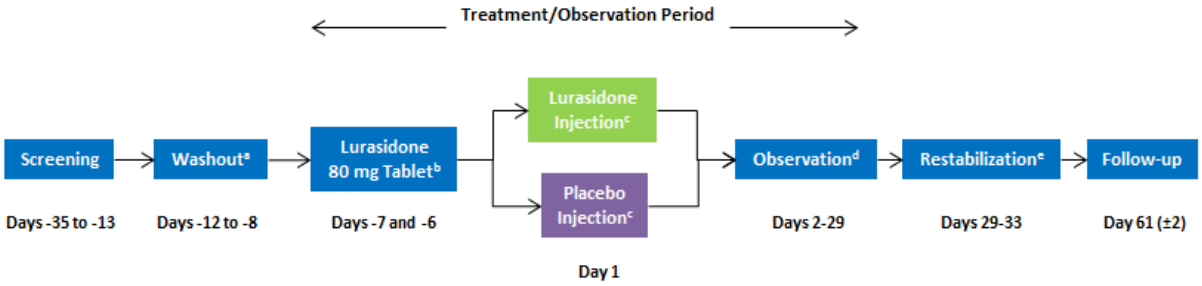
A study schematic is provided below; the schedule of study procedures and assessments is provided in Table 2.

Name of Sponsor: Sunovion Pharmaceuticals Inc.

Name of Investigational Product: Lurasidone injectable suspension

Name of Active Ingredient: Lurasidone (DSP-1349M)

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.

Subjects with schizophrenia who provide informed consent to participate in the study will undergo screening procedures and assessments between Days -35 to -13 to determine study eligibility.

Eligible subjects will be washed out/tapered off of their current antipsychotic medications over 5 to 6 half-lives prior to Day -8 (may begin Day -19). Subjects will be monitored for safety during tapering/washout. Subjects will be admitted to the clinical site on Day -12 and are required to be inpatient until Day 15.

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.

For Cohort 1, a sentinel group of 2 subjects will be dosed in a 1:1 ratio (lurasidone injectable suspension: placebo injection). A 7-day clinical assessment of safety and tolerability (including AEs, vital signs, and other clinically relevant findings) for the sentinel subjects will be made by the Investigator (ie, Day 2 to Day 8). The remaining subjects will be randomized in a 5:1 ratio (lurasidone injectable suspension: placebo injection). A sentinel group may not be required for future dose cohorts: absence of an immune response will obviate the need for sentinel dosing after Cohort 1.

Subjects who are discharged after Day 15 will check into the clinical site again on Days 22 and 29 for scheduled assessments. Subjects will follow protocol procedures to remain in-clinic through Day 33 as they restart their prior medications (including antipsychotics), under observation of the Investigator/clinical site staff (ie, restabilization period).

Subjects who remained in-clinic through Day 29 will remain inpatient through Day 33 as they restart their prior medications (including antipsychotics) under observation of the Investigator/clinical site staff

Name of Sponsor: Sunovion Pharmaceuticals Inc.
Name of Investigational Product: Lurasidone injectable suspension
Name of Active Ingredient: Lurasidone (DSP-1349M)
(ie, restabilization period). The restabilization period may be longer and subjects may remain in-clinic, as deemed necessary by the Investigator. Subjects who discontinue the study prior to Day 29 will undergo assessments scheduled for Day 29 at the time of discontinuation (see Table 2). Subjects who discontinue the study after Day 29 but prior to Day 61 will undergo assessments scheduled for Day 61 at the time of discontinuation (see Table 2). Subjects who complete the study per protocol will return to the clinic for a follow-up safety assessment on Day 61 (± 2). **Dose Escalation/Safety Cohort Review** 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 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. **Determination of the Minimum Intolerable Dose (MID) and Maximum Tolerated Dose (MTD)** The MID will be defined as the dose of Lurasidone injectable suspension at which dose limiting toxicity (DLT) occurs. Dose-limiting toxicity is indicated by the occurrence of intolerable AEs, which are not fully defined a priori, but will be determined from the study data at the SRT meetings. Adverse events, including SAEs, which start prior to the study drug injection, will not be considered for stopping criteria. Dose stopping criteria are provided in Section 9.3. Once a safety stopping criterion is reached, the study will be terminated at that dose level. If none of the stopping criteria has been attained, the study will proceed to the next higher dose level. Dosing of an additional cohort or cohorts at a dose between the identified MID and the highest dose below the MID may be conducted. The highest tolerated dose below the MID will be defined as the MTD for a single lurasidone injectable suspension dose. If the MTD is not established, additional dose cohorts may be commenced until the MTD is reached.
Safety, Pharmacokinetic, and Pharmacodynamic Assessments Safety will be assessed throughout the study by monitoring AE (including injection site reactions),

Name of Sponsor: Sunovion Pharmaceuticals Inc.
Name of Investigational Product: Lurasidone injectable suspension
Name of Active Ingredient: Lurasidone (DSP-1349M)
physical examinations, vital signs (pulse rate, respiration rate, and body temperature), clinical laboratory tests (hematology, serum chemistry, urinalysis, lipid panel, coagulation panel, and thyroid panel), standard 12-lead ECGs, and the Columbia-Suicide Severity Rating Scale (C-SSRS). Blood samples will be collected for serum PK profiling of lurasidone and its 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 after injection dosing at the timepoints specified in the Schedule of Assessments (see Table 2). Serum and urine samples collected for PK assessment may also be used for the additional characterization and/or bioanalytical method development of putative metabolites of lurasidone and for biomarker measurement. The pharmacodynamic impact of lurasidone injectable suspension will be assessed using the Positive and Negative Schizophrenia Symptoms Scale (PANSS).
Number of Subjects (planned): Approximately 8 subjects will be randomized per cohort for a total of up to 40 subjects and up to 5 cohorts. Alternate subjects may be admitted to the clinical site in order to ensure that 8 subjects are dosed in each cohort. Subjects who are randomized but not dosed will be replaced by the alternate subject(s). 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).
Main Diagnosis and Criteria for Enrollment Adult male and female subjects 18 to 65 years of age, inclusive with a diagnosis of schizophrenia as per DSM-IV-TR criteria, which in the opinion of the Investigator has been clinically stable for the 6 months prior to Screening. Subjects must also be able and willing to remain off of prior antipsychotic medication until the protocol-specified restabilization period. Subjects must also have a stable living arrangement for at least 3 months prior to Study Day -12 and agree to return to a similar living arrangement after clinic discharge. Chronically homeless subjects should not be enrolled. The Medical Monitor should be consulted for individual cases as needed. Subjects will not be eligible if they have a known history of severe reaction to a previous antipsychotic (in the Investigator's opinion) including up to 80 mg/day of oral lurasidone, or a history of drug-dependence (per DSM-IV-TR) criteria during the 6-month period prior to Screening, or if they answer "yes" to "Suicidal Ideation" Items 4 or 5 on the C-SSRS at Screening or at any point prior to randomization or history of suicidal behavior within the last two years. Subjects will not be eligible if they have had an acute exacerbation of psychiatric symptoms requiring change in antipsychotic medication (with reference to drug or dose) within 3 months (90 days) before screening. The complete listing of study eligibility criteria is provided in Section 7.
Investigational Product, Dosage and Mode of Administration Lurasidone injectable suspension will be provided as sterile white to off-white aqueous suspension (150 mg/mL lurasidone) for intramuscular injection. The suspension will be packaged in clear USP Type I glass vials with rubber stoppers. A starting dose of 30 mg (0.2 mL lurasidone injectable suspension) will be given. Lurasidone injectable suspension will be administered to subjects using syringe and gauge 22-23 needle. The syringe will be covered to maintain blinding.

Name of Sponsor: Sunovion Pharmaceuticals Inc.
Name of Investigational Product: Lurasidone injectable suspension
Name of Active Ingredient: Lurasidone (DSP-1349M)
Doses of 75, 150, 300, and 450 mg may be administered (ie, cohorts 2-5).
Duration of Treatment The maximum duration for study participation for each subject will be up to approximately 96 days. Subjects will receive oral lurasidone 80 mg doses on Days -7 and -6 (one tablet each day) with approximately 240 mL of water. Subjects who tolerate dosing with oral lurasidone 80 mg will receive a single lurasidone injectable suspension or placebo injection dose on Day 1.
Reference Therapy, Dosage and Mode of Administration Lurasidone 80 mg will be provided as the commercially available oral tablet formulation (Latuda®). Placebo for lurasidone injectable suspension will be provided. The solution will be packaged in clear USP Type I glass vials with rubber stoppers. Placebo for lurasidone injectable suspension will be administered to subjects using syringe and gauge 22-23 needle. The syringe will be covered to maintain blinding.
Prior and Concomitant Medications In accordance with the approved product labeling for Latuda (see approved product labeling), lurasidone should not be used concomitantly with a strong CYP3A4 inhibitor (eg, ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil). Lurasidone should not be used concomitantly with a strong CYP3A4 inducer (eg, rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine). A list of strong CYP3A4 inhibitors and inducers included in Section 23, Appendix V). All prior antidepressants and mood stabilizers (eg, lithium, divalproex/valproic acid, carbamazepine) must be discontinued as tolerated and clinically appropriate starting on Day -12. All other psychotropic medication (except as described in Section 9.5.3), including antipsychotic medication, must be discontinued as tolerated and clinically appropriate starting on Day -12 in a manner that is consistent with labeling recommendations and conventional medical practice. Non-psychotropic medications used to treat mild, chronic medical conditions may be used during Screening and after assignment of a subject number, if the dose and regimen have been stable (± 25%) for at least 30 days prior to Screening. The concomitant medication dose may change as needed after a subject number is assigned (or be discontinued). In addition, use of nonprescription pain medications are allowed during all phases of the study provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study medication. Medications for short-term treatment of a medical condition (no more than 10 days) are allowed with consultation with the Medical Monitor, provided that the medications are not drugs that prolong the QT/QTc interval or CYP3A4 inhibitors or inducers (see Section 22, Appendix IV and Section 23, Appendix V, respectively). During the washout, treatment and post-treatment periods, treatment with benztropine (up to 6 mg/day) will be permitted as rescue medication and as treatment for movement disorders. In cases where benztropine is not available or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute extrapyramidal symptoms (EPS): biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Treatment with amantadine (up to 300 mg/day) will be permitted as needed for akathisia. Medications used to treat movement disorders should not be given prophylactically. Medications used for movement disorders should be tapered and discontinued prior to a subject number is assigned but

Name of Sponsor: Sunovion Pharmaceuticals Inc.
Name of Investigational Product: Lurasidone injectable suspension
Name of Active Ingredient: Lurasidone (DSP-1349M)
may be reinstituted if symptoms emerge. In situations where anticholinergic agents or any other agents that may cause sedation are administered, these should be taken at the same time each day and should not be taken within 12 hours of scheduled assessments. When the specified drugs are not available, similar drugs at equivalent dosages will be substituted in consultation with the Medical Monitor. Concomitant use of lorazepam, temazepam, or zolpidem is permitted with the following restrictions: lorazepam is permitted for clinically significant anxiety/agitation or as a sedative/hypnotic up to a maximum daily dose of 6 mg/day. Intramuscular lorazepam is permitted up to 4 mg/day for acute anxiety/agitation, as clinically indicated. Lorazepam should be used sparingly, when clinically required, per Investigator judgment. Zolpidem (≤ 10 mg in any 24-hour period) and temazepam (≤ 30 mg in any 24-hour period) may be administered, as needed, as sedatives/hypnotics. Hypnotic agents should be administered no more than once nightly and should not be used in combination. Medications used for the as-needed (PRN) treatment of anxiety/agitation and insomnia (eg, lorazepam and zolpidem) should not be used in close temporal proximity (defined as administration within 2 hours of each other). When lorazepam or zolpidem or other specified medications are not available, another similar agent at equivalent doses will be permitted as specified by the Medical Monitor. Opiates may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor. Subjects who require treatment with one or more of the medications listed in Section 22, Appendix IV or Section 23, Appendix V should be excluded or discontinued (as appropriate) from the study. Since these lists of drugs are not comprehensive, Investigators should use medical judgment when a subject presents with a medication not on the list or consult with the Medical Monitor for clarification. A complete listing of permitted medications and therapies, including rescue medications, as well as a complete listing of prohibited medications are provided in Section 9.5.

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Name of Investigational Product: Lurasidone injectable suspension

Name of Active Ingredient: Lurasidone (DSP-1349M)

Criteria for Evaluation:

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 heart 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)

Pharmacokinetic Endpoints

- PK parameters for lurasidone after Lurasidone injectable suspension Administration

  Serum: C_{max}, t_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, λ_z, $t_{1/2}$, CL/F, and V_z/F

  Urine: $Ae_{0\text{-}144h}$, fe, and CL_R
- PK parameters for metabolites after Lurasidone injectable suspension Administration

  Serum: C_{max}, t_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$, λ_z, $t_{1/2}$, metabolite to parent ratio of $AUC_{0\text{-}inf}$ ($MRAUC_{0\text{-}inf}$), and C_{max} (MRC_{max}) for ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220

  Urine: $Ae_{0\text{-}144h}$ for ID-14283, ID-14326, and ID-11614

Pharmacodynamic Endpoint

- Change from baseline, and placebo-corrected change from baseline in Positive and Negative Syndrome Scale (PANSS) total score

Statistical Methods

Safety Analyses

The safety analysis will be conducted by the treatment received using the Safety population, which will consist of all subjects who are randomized and receive study drug. AEs and all other safety data will be listed and summarized descriptively by treatment group (dose level of Lurasidone injectable suspension and placebo) in tabular or graphical formats, as appropriate. Subjects dosed with placebo will be analyzed as a pooled group. Observed values, as well as change from baseline for clinical safety laboratories, vital signs, and ECGs will be listed and summarized descriptively in tabular or graphical 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 summarized.

Pharmacokinetic Analyses

The PK analysis will be conducted on the PK population, which will consist of all subjects who are randomized and receive Lurasidone injectable suspension, have at least one measurable postdose concentration, and have had no relevant protocol deviations or documented reason that a PK profile was unreliable. Subjects will be analyzed according to treatment received. Serum and urine concentrations

Name of Sponsor: Sunovion Pharmaceuticals Inc.
Name of Investigational Product: Lurasidone injectable suspension
Name of Active Ingredient: Lurasidone (DSP-1349M)
and PK parameters for Lurasidone injectable suspension and its metabolites will be listed and summarized descriptively by dose level and subdivided by gender in tabular or graphical formats, as appropriate. Descriptive summaries will include number of subjects, mean, standard deviation, coefficient of variation (CV%), minimum, median, maximum, geometric mean, and geometric CV%. C_{max}, t_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ for Lurasidone injectable suspension will be the primary PK parameters and all others will be secondary PK parameters. Dose proportionality of Lurasidone injectable suspension will be assessed using a power model for C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ of Lurasidone injectable suspension with a formula of ln (PK parameter) = $\alpha + \beta \cdot \ln$ (dose level). The estimate of the slope (β), together with its 90% confidence interval (CI) will be calculated from the model. Dose proportionality assessment will be performed for the dose range studied. <u>Pharmacodynamic (PD) Analyses</u> The pharmacodynamic variable is change from baseline in PANSS total score. The pharmacodynamic variable will be analyzed by mixed model for repeated measures (MMRM) method. The MMRM model will include treatment, time, baseline score, and treatment-by-time interaction. <u>Sample Size:</u> 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.

Table 2: Schedule of Assessments

Study Period	Screen	Washout/Taper[a]		Treatment/Observation[a]									Restabilization[a]			Follow-up
Study Day	**-35 to -13**	**-12**	**-11 to -9**	**-8**	**-7**	**-6**	**-5 to -1**	**1**	**2-8**	**9-14**	**15**	**22**	**29**	**30-32**	**33**	**61 ± 2**
Procedures/Assessments																
Obtain Informed Consent	X															
Review Inclusion/ Exclusion Criteria	X			X												
Record Medical and Psychiatric History	X															
Record Demographics	X															
Perform Physical Examination	X	X		X							X		X		X	X
Record Height	X															
Record Weight and BMI	X			X									X		X	X
Obtain Vital Sign Measurements[b]	X	X		X	X	X	X	X	X	X	X	X	X		X	X
Perform 12-Lead ECG[c]	X	X		X	X	X		X	X	X	X	X	X		X	X
Clinical Laboratory Tests[d]	X			X				X	X		X	X	X		X	X
Serum Prolactin[e]	X			X				X	X		X	X	X		X	X
Serology	X															
Serum Pregnancy Test (females)	X	X		X									X			
Urine Drug Screen	X	X		X									X			
Urine Alcohol Test	X	X		X									X			
Blood Samples for PK[f]					X	X		X	X		X	X	X			X
Urine Samples for PK[g]								X	X							
Psychotropic Medications[h,i]		X											X	X	X	
Administer Columbia-Suicidality Severity Rating Scale (C-SSRS)[j]	X			X	X		X	X	X		X	X	X		X	X
Administer Positive and Negative Syndrome Scale (PANSS)[k]	X				X			X	X		X	X	X			
Clinical Site Admission[a]		X											X			

Table 2: Schedule of Assessments (Continued)

Study Period	Screen	Washout/Taper[a]		Treatment/Observation[a]									Restabilization[a]			Follow-up
Study Day	**-35 to -13**	**-12**	**-11 to -9**	**-8**	**-7**	**-6**	**-5 to -1**	**1**	**2-8**	**9-14**	**15**	**22**	**29**	**30-32**	**33**	**61 ± 2**
Procedures/Assessments																
Awaken Subject			X	X	X	X	X	X	X	X	X	X	X	X	X	
Provide Meals[l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomize Subject								X								
Dispense Oral Lurasidone					X	X										
Oral Lurasidone Administration[m]					X	X										
Dispense Lurasidone or Placebo Injection								X								
Lurasidone or Placebo Injection Administration								X								
Investigator Injection Site Safety Assessment[n]								X	X	X	X	X	X			
Subject Injection Site Pain Assessment[o]								X	X		X	X	X			
Schedule Next Visit	X										X	X			X	
Clinical Site Discharge[p]											X	X			X	
Concomitant Medications[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pretreatment Events	X	X	X	X												
Adverse Events[r]					X	X	X	X	X	X	X	X	X	X	X	X

Note: Subjects who discontinue the study prior to Day 29 will undergo assessments scheduled for Day 29 at the time of discontinuation. Subjects who discontinue the study after Day 29 but prior to Day 61 will undergo assessments scheduled for Day 61 at the time of discontinuation.

[a] Eligible subjects must be washed out/tapered off of their current antipsychotic medications within 5 to 6 half-lives prior to Day -8 (may begin Day -19). Mandatory inpatient periods are Day -12 to Day 15 (for treatment and observation) and Day 29 to Day 33 (for restabilization to previous medications; restabilization begins Day 29). Subjects may remain inpatient until Day 33 at the Investigator's discretion.

[b] Vital signs = Blood pressure (supine and standing), pulse rate (supine and standing), respiration rate, and body temperature will each be collected at the following times

- Day -12 and Day -8: once daily
- Days -7 and -6: predose and 2 hours postdose
- Day -1
- Day 1 pre-injection dose and 6 and 12 hours post-injection dose
- Days 3, 5, 7, 9, 11, 13, and 15 (time-matched to the predose timepoint on Day 1), and Days 22, 29, and 33 (approximately time-matched to the predose timepoint on Day 1), and Follow-up.

Note: Supine blood pressure and pulse rate should be collected at the same time as 12-lead ECG (when 12-lead ECG is collected for the same timepoint). A window of ± 10 minutes of scheduled time is allowed. After Cohort 1, timepoints for vital signs may be changed based on observed t_{max} of Lurasidone injectable suspension and its metabolites.

[c] Standard 12-lead ECGs will be collected at Screening and during the washout/taper period on Days -12 and -8. On Days -7 and -6, standard 12-lead ECGs will be collected predose and 2 hours postdose. Standard 12-lead ECGs will be collected predose and 6, and 12 hours post injection dose on Day 1 and on Days 3, 5, 7, 9, 11, 13, and 15 (time-matched to the predose timepoint on Day 1), and Days 22, 29, and 33 (approximately time-matched to the predose timepoint on Day 1), and Follow-up. A window of ± 15 minutes of scheduled time is allowed for ECGs performed up to and including Day 15. After Cohort 1, these timepoints may be changed based on observed t_{max} of Lurasidone injectable suspension and its metabolites.

[d] Hematology, Serum Chemistry, Urinalysis, Lipid Panel, Coagulation Panel, and Thyroid Panel.

- Subjects are to fast ≥ 8 hours prior to blood sample collection for clinical laboratory tests.
- Blood samples will be collected for Hematology and Serum Chemistry at screening, Day -8, Day 1 injection predose , Days 8 and 15 (time-matched to the predose timepoint on Day 1), and Days 22, 29, and 33 (approximately time-matched to the injection predose sample on Day 1), and follow-up. A window of ± 10 minutes is allowed for clinical laboratory test sample collection. Samples will be obtained at the same time that other blood and urine samples are taken whenever possible.
- Blood samples for thyroid panel, coagulation panel, and lipid panel will be collected at Screening, Day -8 , Day 1 injection predose , Day 15 (time-matched to the predose timepoint on Day 1), and Day 29 (approximately time-matched to the injection predose sample on Day 1).
- Urinalysis will be collected at screening, Day -8, Day 1 injection predose (time-matched to the predose timepoint on Day 1), Days 8 and 15 (time-matched to the predose timepoint on Day 1), and Days 22, 29, and 33 (approximately time-matched to the injection predose sample on Day 1), and follow-up.

[e] Serum Prolactin levels will be blinded, except at screening and Day 1. Designated unblinded medical site staff will be notified if prolactin concentrations are > 200 ng/mL. Blood samples will be collected on Day -8, Day 1 injection predose, Days 8 and 15 (time-matched to the predose timepoint on Day 1), and Days 22, 29, and 33 (approximately time-matched to the injection predose timepoint on Day 1), and follow-up.

[f] Blood samples for serum PK assessment will be collected at predose and 2 hours postdose on Days -7 and -6, and then at 0 hour (predose), 2, 4, 6, 12, 24, 48, 72, 96, 120, 144, 336, 504, 672, and 1440 (± 48) hours after the injection dose given on Day 1. A window of ± 5 minutes of scheduled time (up to 8 hours postdose), and ± 10 minutes of scheduled time (from 12 hours postdose onward) is allowed. Blood sampling timepoints for PK assessment for subsequent cohorts may be modified based on serum concentration data from initial cohort(s). Evaluation of the relationship between the timing of below limit of quantification (BLQ) and the elimination half-life will be used to justify the revised blood sampling for PK and safety assessment schedule.

[g] Urine samples for PK assessment will be collected at the following intervals: -0.5 to 0 hour (predose); 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, and 120 to 144 hours after the injection dose given on Day 1, and recording of the volume of urine sample at each time interval. Urine samples collected for PK analysis may also be used for the additional characterization and/or bioanalytical method development of putative metabolites of DSP-1349M and for biomarker measurement, if needed.

[h] Tapering of patient's psychotropic medications prior to entry to the study has been done routinely in previously conducted studies with lurasidone. The exact timing and method of taper will depend on the subject's medication regimen, but the tapering process will typically start approximately one week prior to Day -12 admission. However, for some subjects, the tapering process will begin sooner than one week and some may begin later than one week from Day -12 admission based on PI's evaluation.

[i] Restabilization' refers to the reintroduction of each subject's prior medications that were taken prior to entry into the study including their psychotropic medications. The inpatient restabilization for reintroduction of prior medications including psychotropics may be longer, if needed. For early termination patients who received lurasidone dosing, following follow-up procedures they will need to be restabilized following the restabilization procedures.

[j] The C-SSRS will be administered at Screening, during the Treatment/Observation period on Day -8 (ie, pre-oral dosing), Day -7 (postdose), Day -1 (pre-injection dose), Day 1 (postdose), and Days 7, 15, 22, and 29, at the end of restabilization on Day 33, and at follow-up Day 61 ± 2. The Screening/Baseline and Since Last Visit Versions of the C-SSRS will be utilized in this study.

[k] PANSS will be administered once during Screening, and on Days -7, 1 (predose), 8, 15, 22, and 29.

[l] Lunch will be provided ≥ 4 hours postdose on Days -7, -6 and 1. Standard meals will be provided during the inpatient period and outpatient clinic return visits on when applicable.

[m] Subjects will fast overnight for at least 8 hours on Day -8 and Day -7. On Days -7 and -6, standard breakfast (minimum 350 calories) will be served 30 minutes prior to the planned dosing time. Dosing of lurasidone 80 mg orally will take place 30 minutes after the start of breakfast. Subjects will receive dose administration at approximately the same time on each day of dosing during the study. Lurasidone 80 mg will be administered with approximately 240-mL water on Days -7 and -6. Water intake is restricted for one hour before and two hours after dose administration; after which water will be allowed *ad libitum*. Subjects will fast for 4 hours after dosing on Day -7 and on Day -6.

[n] Investigator injection site safety assessment will include a rating of 1-4 on each of 4 items (pain, tenderness, erythema/redness, and induration/swelling). Assessments will be made on Day 1 (immediately after injection, and 6 hours and 12 hours after injection), Day 2 (24 hours after injection), Days 3-15 (daily during the inpatient period), Day 22, and Day 29. A window of +1 minute is allowed for the immediately after injection timepoint, and a window of ± 5 minutes is allowed for the 6 and 12 hour timepoints on Day 1. In addition subjects will be monitored for potential allergic reaction for 15 minutes after injection. A window of 0-5 minutes is allowed for the evaluation of potential allergic reaction.

[o] Subjects will assess their injection site pain using a rating of 0-10 on a Likert Scale (0 = no pain, 10 = worst pain). This assessment will be completed prior to the Investigator injection site assessment on Day 1 (immediately after injection, and 6 hours and 12 hours after injection), Day 2 (24 hours after injection), Day 8, Day 15, Day 22, and Day 29. A window of +1 minute is allowed for the immediately after injection timepoint, and a window of ± 5 minutes is allowed for the 6 and 12 hour timepoints on Day 1.

[p] Alternate subjects not included in the study cohort will be discharged following reintroduction of their prior medication if they are clinically stable (in the Investigator's opinion), subjects who received study drug will be eligible for discharge on Day 15 (but may remain inpatient at the Investigator's discretion up to Day 33), and early withdrawal subjects will be discharged after follow-up assessment procedures.

[q] Concomitant medications will be recorded prior to and after oral and injection dosing.

[r] In addition to any untoward medical occurrences in the subject (pre and postdose on dosing days), assessment of the injection site and monitoring of prodromal symptoms for seizures will be performed. If prodromal symptoms for seizure are found, additional neurological assessments will be done, as needed.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The abbreviations and the definition of key study terms used in the clinical study protocol are shown in Table 3 and Table 4.

Table 3: List of Abbreviations

Abbreviation	Full Form
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CFR	Code of Federal Regulations
CI	Confidence Interval
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case report form (or electronic case report form)
CRO	Contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	Coefficient of variation
ECG	Electrocardiogram
EDC	Electronic data capture
EPS	Extrapyramidal symptoms
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
hCG	Human chorionic gonadotropin
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IPD	Important protocol deviation
IRB	Institutional Review Board
IUD	Intrauterine device
IXRS	Interactive Voice/Web-based Response System
MedDRA	Medical Dictionary for Regulatory Activities

Table 3: List of Abbreviations (continued)

Abbreviation	Full Form
MMRM	Mixed model for repeated measures
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic(s)
PR	Time between P wave and QRS in electrocardiography
PT	Preferred term
PVG	Pharmacovigilance
QRS	Electrocardiographic wave (complex or interval)
QT	Electrocardiographic interval from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SOP	Standard Operating Procedure
SRT	Safety review team
US	United States

Table 4: Definition of Key Study Terms

Terms	Definition of terms
CRF	A printed, optical, or electronic document designed to record all of the protocol required information to report to the Sponsor for each study subject.
Screened Subject	Any subject who signed the study specific informed consent and completed at least one study related procedure.
Screen Failures	Any subject who signed the study specific informed consent but either failed to meet study requirements during screening or met study requirements at screening but was not enrolled/randomized.
Study Drug (or Study medication)	Term to cover investigational drug, placebo, and/or active control.
Treatment Period	The period of the study in which the study drug is administered.
Randomized Subject	Any subject who was randomized into the treatment period of the study and was assigned a randomization number.
Enrolled Subject	Any subject who was successfully screened and enrolled into the pre-randomization period of the study.
Randomization Failures	Any subject who was enrolled but not randomized.
Completed Subject	Any subject who participated throughout the duration of the study, up to and including Day 29.
Early Termination Subject	Any subject who was successfully screened and randomized into the treatment period of the study, but did not complete the study.
End of Treatment	The day that the subject receives the protocol-defined last dose of the study drug.
End of Study	The day of the last visit by the last subject in the study.

3. INTRODUCTION

3.1. Background

Lurasidone injectable suspension (DSP-1349M) is a novel compound synthesized by Sumitomo Dainippon Pharma Co., Ltd., as a candidate psychotropic agent for the treatment of patients with schizophrenia. It possesses high affinities for dopamine D2, serotonin 5 HT2A, 5 HT7, 5 HT1A and noradrenaline α2C receptors. Compared with other atypical antipsychotics, lurasidone demonstrates similar binding affinities for the D2 and 5 HT2A receptors, but greater affinity for serotonin 5 HT1A receptors. Lurasidone displays no affinity for histamine H1 or acetylcholine M1 receptors.

Lurasidone has a unique chemical structure that differs from conventional antipsychotic therapies such as the phenothiazine, butyrophenone, and benzamide classes of antipsychotic agents. The chemical name is (3aR,4S,7R,7aS)-2-{(1R,2R)-2-[4-(1,2-benzisothiazol-3 yl)piperazin-1-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-1,3-dione hydrochloride. Due to its serotonin 5 HT2 blocking actions, lurasidone is associated with fewer extrapyramidal symptoms (EPS) than conventional antipsychotic therapeutic agents and is effective in ameliorating the positive and negative symptoms of schizophrenia. In preclinical pharmacological studies, lurasidone has been shown to be effective in various animal models of schizophrenia and to have weak potential for inducing EPS.

In general, the slow release characteristics (pharmacokinetics) of several current long acting injectable antipsychotics is attributed to either the rate of hydrolysis of the ester form of the antipsychotic molecule by esterases in muscle or to the slow rate of diffusion of the esterified antipsychotic from an oil vehicle. In contrast, injectable lurasidone is the free base of lurasidone hydrochloride that is placed in an aqueous solution as a suspension. Free base lurasidone has very low solubility in aqueous solution, so when injected into muscle, dissolution of freebase lurasidone in a limited aqueous surrounding governs the clearance from muscle into serum.

Schizophrenia is a severe psychiatric disorder that has a profound effect on both the individuals affected and society (Owen, 2016). Schizophrenia occurs at an incidence of roughly 15 men and 10 women per 100,000 populations per year, a point prevalence of 4.6 per 1,000, and a lifetime morbid risk of around 0.7% (McGrath, 2008). A coherent body of evidence from pharmacological and brain-imaging studies implicates dysfunction of dopaminergic neurotransmission in the genesis of psychotic symptoms such as delusions and hallucinations (Howes, 2014).

Unemployment in people with schizophrenia is 80% to 90% (Marwaha, 2004), and in 2013, the estimated societal economic burden of schizophrenia was estimated to be approximately $156 billion in the US (Cloutier, 2016).

Mortality from most natural causes, especially cardiovascular disorders, is the strongest contributor to the 10 to 20 year reduction in life expectancy (Chesney, 2014). There is a clear need to develop antipsychotic compounds with reduced side effects, particularly those affecting metabolic processes that result in adverse cardiovascular outcomes (Miyamoto, 2012).

3.2. Study Conduct Rationale

Non-adherence in medication-taking remains one of the major challenges in the treatment of any chronic illness such as schizophrenia. Numerous studies have found high levels of non-adherence in medication taking in patients with schizophrenia. One potentially valuable approach to enhancing adherence is the use of long-acting injectable antipsychotic medications.

This study is being conducted to evaluate the safety and tolerability of a single intramuscular (IM) injection of lurasidone injectable suspension (DSP-1349M) in adult subjects. This study will also determine the pharmacokinetic (PK) characteristics of lurasidone and its metabolites in serum and urine after single IM dose administration of lurasidone injectable suspension.

3.3. Risk-Benefit Assessment

The potential risks anticipated based on lurasidone clinical studies and lurasidone injectable suspension nonclinical studies conducted to date are amenable to detection via safety monitoring in this study (consisting of adverse event reporting, injection site reactions, vital sign assessments, electrocardiograms monitoring, clinical laboratory evaluations, physical examinations, and discontinuation summaries). The 28-day observation period after injection dosing is considered clinically appropriate for monitoring safety and tolerability. Similarly, the 28-day observation/follow-up period after restabilization (ie, subjects re-starting their prior medications) is considered clinically appropriate for safety monitoring and to ensure subjects are clinically stable.

4. STUDY OBJECTIVES

4.1. Safety Objective

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

4.2. Pharmacokinetic and Pharmacodynamic Objectives

- 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.

5. STUDY ENDPOINTS

5.1. 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)

5.2. Pharmacokinetic Endpoints

- PK parameters for lurasidone after Lurasidone injectable suspension Administration
  - Serum: C_{max}, t_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, λ_z, $t_{1/2}$, CL/F, and V_z/F
  - Urine: $Ae_{0\text{-144h}}$, fe, and CLR
- PK parameters for metabolites after Lurasidone injectable suspension Administration
  - Serum: C_{max}, t_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, λ_z, $t_{1/2}$, metabolite to parent ratio of $AUC_{0\text{-inf (MRAUC0-inf)}}$, and $C_{max\ (MRCmax)}$ for ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220
  - Urine: $Ae_{0\text{-144h}}$ for ID-14283, ID-14326, and ID-11614

5.3. Pharmacodynamic Endpoint

- Change from baseline, and placebo-corrected change from baseline in Positive and Negative Syndrome Scale (PANSS) total score

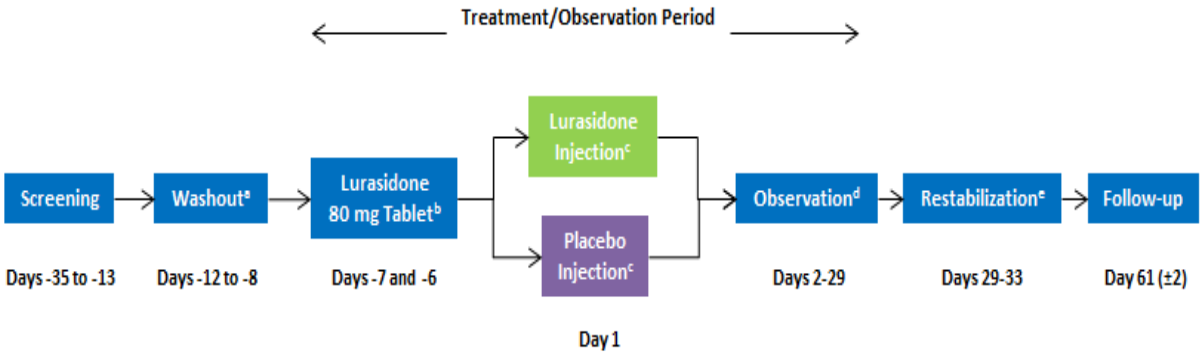
6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

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.

A study schematic is presented in Figure 1. Details of the study assessments and other procedures to be performed at each visit are presented in Table 2, Schedule of Assessments, and Section 10, Study Assessments. The maximum duration for study participation for each subject will be up to approximately 96 days. If necessary, subjects may return to the clinic at any time for an unscheduled visit.

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.

Subjects with schizophrenia who provide informed consent to participate in the study will undergo screening procedures and assessments between Days -35 to -13 to determine study eligibility.

Eligible subjects will be washed out/tapered off of their current antipsychotic medications over 5 to 6 half-lives prior to Day -8 (may begin Day -19). Subjects will be monitored for safety during tapering/washout. Subjects will be admitted to the clinical site on Day -12 and are required to be inpatient until Day 15.

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.

Subjects who are discharged after Day 15 will check into the clinical site again on Days 22 and 29 for scheduled assessments. Subjects will follow protocol procedures to remain in-clinic through Day 33 as they restart their prior medications (including antipsychotics), under observation of the Investigator/clinical site staff (ie, restabilization period).

Subjects who remained in-clinic through Day 29 will remain inpatient through Day 33 as they restart their prior medications (including antipsychotics) under observation of the Investigator/clinical site staff (ie, restabilization period).

The restabilization period may be longer and subjects may remain in-clinic, as deemed necessary by the Investigator.

Subjects who discontinue the study prior to Day 29 will undergo assessments scheduled for Day 29 at the time of discontinuation (see Table 2). Subjects who discontinue the study after Day 29 but prior to Day 61 will undergo assessments scheduled for Day 61 at the time of discontinuation (see Table 2).

Subjects who complete the study per protocol will return to the clinic for a follow-up safety assessment on Day 61 (± 2).

6.2. Treatment Assignment and Blinding

6.2.1. Treatment Assignment

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 (ie, absence of moderate adverse

events). Subjects who tolerate dosing with oral lurasidone 80 mg will be eligible for randomization 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 at the ventrogluteal site. Subsequent cohorts are planned to be dosed at 75, 150, 300, and 450 mg IM at the ventrogluteal site. 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.

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.

6.2.2. Blinding

This is a double-blind study.

All study drug (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 labeled 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. All study drug (lurasidone injectable suspension or placebo) will be dispensed according to the randomization schedule supplied by the Sponsor or its representative, using a written study drug dispensing procedure that will assure that subjects remain blinded to the treatment being administered.

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.

6.2.3. Emergency Unblinding Procedures

Subject specific unblinding information (eg, individual envelopes) will be generated and stored in secured area in a tamper evident container. The blinded randomization information is to be broken only in an emergency when knowledge of such treatment may have an impact on further treatment decisions or aid in the emergency treatment of the subject. Every effort must be made to contact the Medical Monitor (Table 1) prior to any unblinding of the study drug. The circumstances that lead to the unblinding of treatment assignment are to be promptly communicated via telephone and in writing to the Medical Monitor. Any subject for whom the blind is broken should undergo final evaluation procedures, in accordance with the follow-up visit on Day 61 (± 2) as described in Section 10.5.5.

6.3. Rationale

6.3.1. Rationale for the Study Design

The SAD study design is appropriate for a first-in-human evaluation of the safety, tolerability, and PK of lurasidone injectable suspension.

6.3.2. Rationale for the Dosages

Dosing for the lurasidone injectable suspension formulation is based on the amount in mg of lurasidone present at the injection site following IM administration, which was ~60 mg at the lowest dose of 7.5 mg/kg in the dog. There was no no-observed-adverse effect level determined in the dog; therefore a 2-fold reduction in the amount of lurasidone at the injection site was recommended, which is equal to 30 mg. At the clinical formulation's fixed concentration of 150 mg/mL, this dose will be an injection volume of 0.2 mL.

A 2-fold reduction is considered appropriate because the primary finding of granuloma is common following IM administration of an irritating substance. Clinicians are familiar with appropriate monitoring. This finding is reversible and non-lethal. The pharmacology of lurasidone is well known, and systemic findings in humans have been characterized over a range of serum concentrations.

After the lurasidone injectable suspension starting dose of 30 mg, dose escalation will be as follows: 75, 150, 300, 450 mg for a single IM injection. A 6 week monitoring period for adverse events will be employed in this study. In animals, the injection site findings were apparent within 1 week and findings persisted for an additional week before beginning to resolve. Therefore, if no injection site findings are seen within 2 weeks and no other stopping criteria are met, dose escalation may proceed.

Projection of PK following each cohort indicates that C_{max} will not exceed 348 ng/mL. This value is the C_{max} at 400 mg orally, which is the MTD (Study D1050217, Day 6). It is unlikely that IM administration will exceed this concentration as the depot will absorb more slowly than following oral administration. Therefore, routine safety monitoring will be utilized to determine stopping criteria.

In order to ensure subjects who are unable to tolerate lurasidone do not receive the lurasidone injectable suspension formulation, subjects will be evaluated for tolerability after administration of oral lurasidone 80 mg for 2 days (ie, two doses) prior to lurasidone injectable suspension administration.

The oral lurasidone 80 mg dose was previously established as the maximum tolerated dose (MTD) in healthy subjects. In subjects with schizophrenia, an oral lurasidone dose of 400 mg/day was previously established as the MTD.

6.3.3. Rationale for the Study Population

The subject population includes males and females ranging from 18 to 65 years of age, and in accord with standard practice guidelines, will be required to have a diagnosis of schizophrenia (by DSM-IV-TR).

6.4. Prevention of Missing Data

In an effort to minimize the number of subjects who withdraw consent prior to study completion, the number of visits and assessments has been limited to those required to collect the information needed to address the objectives of the study. Evaluation of safety and tolerability is essential for this study population, therefore, at the Investigator's discretion, subjects may be inpatient during the washout/taper period as well as after the treatment/observation period. Obtaining PK samples postdose is an essential component of the study; therefore, subjects will remain in the clinic for the duration of the blood samples collection for serum PK assessment, and a concerted effort by the clinical site will be made to enroll and randomize subjects with good venous access. In addition, every effort will be made to have subjects complete follow-up safety contact.

Refer to Section 14.3.9 for statistical considerations related to missing data.

7. SELECTION OF SUBJECTS

7.1. Subject Inclusion Criteria

Subjects must meet all of the following criteria for inclusion in the study:

1. Subject has capacity; is willing and able to provide written consent for use and disclosure of protected health information per requirements of 45CFR164.508 (Health Insurance Portability and Accountability Act; HIPAA) prior to initiating any study procedure after being informed of the nature of the study, in the opinion of the study staff and PI.
2. Subject is male or female 18 to 65 years of age, inclusive.
3. Subject has a diagnosis of schizophrenia as per DSM-IV-TR criteria, which in the opinion of the Investigator has been clinically stable for the past 6 months.
4. Subject has a Body Mass Index (BMI) greater than or equal to 19.5 and less than or equal to 38 kg/m^2.
5. Subject does not have clinically relevant abnormal laboratory values per Investigator discretion.
6. Subject does not have clinically relevant findings from vital signs measurements per Investigator discretion.
7. Female subject is eligible to enter and participate in the study if she is of:
   a. Non-childbearing potential (ie, physiologically incapable of becoming pregnant, including any female who is pre-menarchal or post-menopausal);
      – Postmenopausal females defined as being amenorrheic for greater than 2 years (or confirmed by FSH level) with an appropriate clinical profile.
      – Women who have not been confirmed as postmenopausal should be advised to use contraception as outlined below.
      – Women who have had a hysterectomy, bilateral oophorectomy or bilateral salpingectomy (as determined by subject's medical history).
   b. Child-bearing potential (all females ≤ 65 years of age), has a negative pregnancy test at screening and agrees to satisfy one of the following requirements:
      – Complete abstinence from intercourse (as part of an abstinent lifestyle) a minimum of 2 months prior to administration of the first dose of study drug, throughout the Treatment Period, and for a minimum of 3 months after completion or premature discontinuation from the study drug; or,
      – Established use of highly effective methods of contraception from 1 month prior to administration of the first dose of study drug, during the Treatment Period, and 60 days after completion or premature discontinuation from the study drug (see Section 9.6).

   • Because of the unacceptable failure rate of barrier (chemical and/or physical) methods, the barrier method of contraception must only be used in combination with a highly effective method. Post-coital methods of contraception are not permitted.

8. Male subjects with partners of child bearing potential must be practicing abstinence, part of an abstinent life style or using protocol-specified methods of birth control throughout the study and for 30 days after completion or premature discontinuation from the study drug.
9. Subject is able and willing to remain off of prior antipsychotic medication until the protocol-specified restabilization period.
10. Subject has a stable living arrangement for at least 3 months prior to Day -12 and agrees to return to a similar living arrangement after discharge. Such subjects remain eligible to participate in this protocol with approval from the PI. Chronically homeless subjects should not be enrolled. The Medical Monitor should be consulted for individual cases as needed.

7.2. Subject Exclusion Criteria

The subjects who meet any of the following criteria will be excluded in the study.

1. Subject had an acute exacerbation of psychiatric symptoms requiring change in antipsychotic medication (with reference to drug or dose) within 3 months (90 days) before screening.
2. Subject has known or suspected carcinoma.
3. Subject has known presence or history of renal or hepatic insufficiency.
4. Subject has significant disease(s) or clinically significant finding(s) on physical examination determined by the Investigator to pose a health concern to the subject while on study.
5. Subject has a history or presence of clinically significant abnormal ECG (based on ECG central overread report) that may jeopardize the subject's safety to participate in this study, or a screening 12-lead ECG demonstrating any one of the following: heart rate (HR) > 100 bpm, QRS > 120 msec, QTcF > 450 msec, or PR > 220 msec.
6. Subject has known history of a severe reaction to a previous antipsychotic (in the Investigator's opinion), including up to 80 mg/day of oral lurasidone.
7. Subject has a history of drug-dependence as per DSM-IV-TR criteria during the six month period immediately prior to study entry.
8. Subject has known or suspected excessive alcohol consumption, (exceeding more than 4 drinks on any single day or more than 14 drinks per week; 1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of the screening visit or a positive urine alcohol test at screening.
9. Subject answers "yes" to "Suicidal Ideation" Items 4 or 5 on the C-SSRS at screening (in the past 1 month [30 days]) or at any point prior to randomization or history of suicidal behavior within the last two years.
10. Subject has significant orthostatic hypotension at screening (ie, a drop in systolic blood pressure of 30 mmHg or more and/or drop in diastolic blood pressure of 20 mmHg or more on standing).

11. Subject has presence or history (within the last year) of a medical or surgical condition that might interfere with the absorption, metabolism, or excretion of administered Lurasidone injectable suspension.
12. Subject has a history of epilepsy or risk of having seizures.
13. Subject has a positive urine alcohol at screening or on Day -12.
14. Subject has positive test results within 28 days prior to the start of the study for:
    a. Human immunodeficiency virus (HIV).
    b. Hepatitis B surface antigen and Hepatitis C antibody.
    c. Urine drug test (marijuana, amphetamines, barbiturates, cocaine, opiates, benzodiazepines, methadone, or other drugs of abuse). However, a positive test for benzodiazepines may not result in exclusion of subjects if the Investigator determines that the use of a prescription benzodiazepine is appropriate.
    d. Serum β-human chorionic gonadotropin (HCG) consistent with pregnancy (females only).
15. Subject has used of any inhibitor or inducer of CYP3A4 taken within 28 days prior to drug administration and until discharge.
16. Subject has have used of concomitant medications that prolong the QT/QTc interval within 28 days prior to Day -12 through follow-up.
17. Subject has received depot neuroleptics unless the last injection was at least one treatment cycle before Day -12.
18. Subject has poor peripheral venous access or does not tolerate venipuncture that would cause difficulty for collecting blood samples.
19. Subject has experienced significant blood loss (≥ 473 mL) or donated blood within 30 days prior to screening, or intends to donate plasma or blood or undergo elective surgery during study participation or within 30 days after the last study visit.
20. Subject has a prolactin concentration greater than or equal to 200 ng/mL at screening.
21. Subject is unwilling to abstain from vigorous exercise from Day -12 until study discharge.
22. Subjects has a significant risk of violent behavior or a significant risk of suicidal behavior based on history or in the PI's judgment OR is considered by the Investigator to be at imminent risk of suicide or injury to self, others, or property.
23. Subject has a history of allergic reaction (clinically relevant history of drug hypersensitivity) or has a known or suspected sensitivity to any substance that is contained in the study drug or to Polysorbate 80, sodium chloride, or sodium phosphate.
24. Subject requires treatment with a drug that consistently prolongs the QTc interval (see Section 22, Appendix IV).
25. Subject is currently participating, or has participated in a study with an investigational or marketed compound or device within 30 days prior to signing the informed consent, or

has participated in 3 or more studies within 18 months prior to signing the informed consent.

26. Subject is a staff member or the relative of a staff member.
27. Subject, in the Investigator's opinion, is unsuitable in any other way to participate in the study.
28. Subject is unable or unwilling to comply with study instructions, procedures or restrictions.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Description of Study Drug

Reference Therapy Lurasidone 80 mg will be provided as film-coated tablet formulation as commercially available Latuda 80 mg tablets.

Lurasidone injectable suspension will be provided as sterile white to off-white aqueous suspension (150 mg/mL lurasidone) for intramuscular injection. The suspension will be packaged in clear USP Type I glass vials with rubber stoppers.

A starting dose of 30 mg (0.2 mL lurasidone injectable suspension) will be given. Lurasidone injectable suspension will be administered to subjects using syringe and gauge 22-23 needle. The syringe will be covered to maintain blinding.

Doses of 75, 150, 300, and 450 mg may be administered (ie, cohorts 2-5).

Placebo injection will be provided as sterile clear aqueous solution for intramuscular injection. The solution will be packaged in clear USP Type I glass vials with rubber stoppers.

Placebo for lurasidone injectable suspension will be administered to subjects using syringe and gauge 22-23 needle. The syringe will be covered to maintain blinding.

Table 5: Investigational Product

Attribute	Investigational Product	
Product name	Lurasidone Injectable Suspension 150 mg/mL	Placebo Injection 150 mg/mL
Dosage form	Injectable suspension	Injectable solution
Route of administration	Intramuscular injection	Intramuscular injection
Physical description	Sterile white to off-white aqueous suspension	Sterile clear aqueous solution
Excipients	Polysorbate 80, sodium chloride, monobasic sodium phosphate and dibasic sodium phosphate, and Water for Injection	

8.2. Study Drug Packaging and Labeling

8.2.1. Package Description

Reference therapy Lurasidone 80 mg film-coated tablets will be packaged in HDPE bottles as market product of Latuda®.

Lurasidone injectable suspension will be packaged, with pre-filled volume of 1.25 mL, in a clear USP Type I glass vials with rubber stoppers and sealed. The vials will be stored in a carton with dividers.

Placebo for Lurasidone injectable suspension will be packaged with pre-filled volume of 1.25 mL, in a clear USP Type I glass vials with rubber stoppers and sealed. The vials will be stored in a carton with dividers.

8.2.2. Labeling Description

All labeling and packaging for study drug will be based on all applicable regulatory requirements described in the United States (US) Code of Federal Regulations (CFR), CRF21, Part 312.6. Label text may include, but is not limited to, the following information:

- Protocol number
- Sponsor's name and address
- Contents (eg number of tablets, strength)
- Instructions for use and storage
- Lot number
- Unique medication number (if needed)

8.3. Study Drug Storage

Lurasidone oral tablets are to be stored at 25°C (77°F); excursions permitted to 15° - 30°C (59° F to 86°F).

Lurasidone injectable suspension and placebo for injection are to be stored at 20-25°C (68-77°F).

8.4. Dispensing of Study Drug

Unblinded clinical site pharmacist will prepare and quality check each injection dose for each subject per provided pharmacy manual, randomization schedule, and other applicable local regulations as set forth in the protocol. The unblinded site pharmacist will be trained with the pharmacy manual.

8.5. Study Drug Accountability

The Investigator or designee is responsible for storing the drug in a secure location and for maintaining adequate records of drug receipt and disposition that includes the dates, quantity, and use for purposes or by subjects. If the study is stopped for any reason or completed, all unused supplies of drug will be returned to the Sponsor, unless other instructions are provided in writing by Sponsor/CRO.

Upon receipt of study drug, the Investigator or designee will inventory and verify receipt of supplies. The site will perform an acknowledgement of receipt via site established process and per requirements outlined in the pharmacy manual confirming the date of receipt, inventory and condition of study drug received into site source document.

The Investigator or designee will maintain the inventory for accountability, including study drug dispensation, return and availability of study drug received. Established site standards and instructions outlined in the pharmacy manual will provide instruction for the accountability of the study drug at the clinical site.

The drug will not be dispensed to any person who is not a study subject under this protocol.

8.6. Study Drug Handling and Disposal

The Investigator or designee on an ongoing basis must maintain a drug inventory record of supplied, received, dispensed, and returned medication. The Investigator or designee is required to return all unused study drug to the Sponsor or designee, or destroyed as instructed in writing from Sponsor. The Investigator or designee is required to maintain copies of medication shipping receipts, drug accountability records, and records of return or final disposal of the study drug in accordance with local regulatory requirements.

9. TREATMENT OF SUBJECTS

9.1. Study Drug

Lurasidone 80 mg will be provided as the commercially available oral tablet formulation (Latuda®).

Lurasidone and placebo for injection will be supplied as defined in Section 8.2.

Subjects will receive oral lurasidone 80 mg on Days -7 and -6, 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 receive lurasidone or placebo injection on Day 1.

9.2. Dose Escalation/Safety Cohort Review

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 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.

9.3. Determination of the MID and MTD

The MID will be defined as the dose of Lurasidone injectable suspension at which dose limiting toxicity (DLT) occurs. Dose-limiting toxicity is indicated by the occurrence of intolerable AEs, which are not fully defined a priori, but will be determined from the study data at the SRT meetings. The following criteria will be used as a guide:

- If 50% or more of the subjects receiving study drug have either multiple moderate AEs and/or a severe AE possibly related to study drug as determined by the SRT – MID may have been reached, and safety data will be unblinded.
- If more than one subject but less than 50% of the subjects receiving study drug have either multiple moderate AEs and/or a severe AE possibly related to study drug as determined by the SRT – a dose level/cohort may be repeated or a modified escalation may be employed, and safety data of the subject(s) in question will be unblinded.

The SRT may decide to stop dose escalation, repeat a dose, or de-escalate if the number, severity, or type of AEs indicates that higher doses would not be tolerated. In addition, the following stopping criteria for dose-escalation will also be used to assess whether to proceed to a higher dose level in the next cohort. Dose escalation will not occur, although a dose cohort may be repeated or de-escalate if any of the following criteria are met:

- Adverse Events
  - A SAE associated with the use of the study drug with a reasonable possibility that the event may have been caused by the study drug occurs in any subject on active drug.
- Cardiac Parameters
  - A confirmed value of QTcF interval > 500 ms or > 60 ms change from baseline, based on cardiologist over read ECGs occurs in any 2 subjects on active drug.
- Hepatic Parameters
  - Liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or total bilirubin [TBL]) > 3 x upper limit of normal (ULN) occurs in any 3 subjects on active drug.
  - Any one of Hy's law criteria are met for any subject on active drug.
  - ALT or AST > 8 x ULN.
  - ALT or AST > 5 x ULN for more than 2 weeks.
  - ALT or AST > 3 x ULN and (TBL > 2 x ULN or international normalized ratio [INR] > 1.5).
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

- 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

Reference: FDA Guidance for Industry "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials," 2007.

Adverse events, including SAEs, which start prior to study drug injection, will not be considered for stopping criteria.

Once a safety stopping criterion is reached, the study will not escalate beyond that dose level. If none of the stopping criterion has been attained, the study will proceed to the next higher dose level. Dosing of an additional cohort or cohorts at a dose between the identified MID and the highest dose below the MID may be conducted. The highest tolerated dose below the MID will be defined as the MTD for a single lurasidone injectable suspension dose.

If the MTD is not established, additional dose cohorts may be commenced until the MTD is reached.

9.4. Treatment Compliance

This is a single-dose study. Study drug will be administered at the clinical site. The date and time of study drug administration will be recorded.

9.5. Prior and Concomitant Medications

The following information on all concomitant medication administered will be recorded on the CRF and will include medication name, dose, dose unit, frequency, route, start date, stop date, and indication. Any medication or non-pharmacological therapy that is taken by or administered to the subject at any point during the course of this study must be recorded in the eCRF.

Information on the format and version of coding dictionary is provided in the Data Management Plan. All medications will be coded using WHO-DD.

9.5.1. Prior Medications

All prior antidepressants and mood stabilizers (eg, lithium, divalproex/valproic acid, carbamazepine) must be discontinued as tolerated and clinically appropriate starting on Day -12. All other psychotropic medication (except as described in Section 9.5.3), including antipsychotic medication, must be discontinued as tolerated and clinically appropriate starting on Day -12 in a manner that is consistent with labeling recommendations and conventional medical practice.

These prior medications will not be allowed until subjects have completed Day 30.

Initiation of new psychotherapeutic interventions (eg, a new course of psychotherapy) will not be permitted during the study through the restabilization period. Subjects who have participated in ongoing psychotherapy treatment for at least 12 weeks prior to screening will be permitted to continue this treatment during the study.

Additional medication use as specified in the exclusion criteria is prohibited prior to the study.

9.5.2. Concomitant Nonpsychotropic Medications

Non-psychotropic medications used to treat mild, chronic medical conditions may be used during Screening and after assignment of a subject number, if the dose and regimen have been stable (± 25%) for at least 30 days prior to Screening. The concomitant medication dose may change as needed (or be discontinued) after a subject number is assigned. In addition, use of nonprescription pain medications are allowed during all phases of the study provided these medications do not have a propensity for psychotropic effects and do not interfere with the evaluation of study medication. Medications for short-term treatment of a medical condition (no more than 10 days) are allowed with consultation with the Medical Monitor provided that the medications are not drugs that prolong the QT/QTc interval or CYP3A4 inhibitors or inducers (see Section 22, Appendix IV and Section 23, Appendix V, respectively).

9.5.3. Concomitant Psychotropic Medications

During the wash-out, treatment and post-treatment periods, treatment with benztropine (up to 6 mg/day) will be permitted as rescue medication and as treatment for movement disorders. In cases where benztropine is not available or a subject has had an inadequate response or intolerability to benztropine treatment, the following medications may be used to treat acute EPS: biperiden (up to 16 mg/day) or trihexyphenidyl (up to 15 mg/day) or diphenhydramine (up to 100 mg/day). Treatment with amantadine (up to 300 mg/day) will be permitted as needed for akathisia. Medications used to treat movement disorders should not be given prophylactically. Medications used for movement disorders should be tapered and discontinued prior to a subject number is assigned but may be reinstituted if symptoms emerge.

In situations where anticholinergic agents or any other agents that may cause sedation are administered, these should be taken at the same time each day and should not be taken within 12 hours of scheduled assessments. When the specified drugs are not available, similar drugs at equivalent dosages will be substituted in consultation with the Medical Monitor. Concomitant use of lorazepam, temazepam, or zolpidem is permitted with the following restrictions: lorazepam is permitted for clinically significant anxiety/agitation or as a sedative/hypnotic up to a maximum daily dose of 6 mg/day. Intramuscular lorazepam is permitted up to 4 mg/day for acute anxiety/agitation, as clinically indicated. Lorazepam should be used sparingly, when

clinically required, per Investigator judgment. Zolpidem (≤ 10 mg in any 24-hour period) and temazepam (≤ 30 mg in any 24-hour period) may be administered, as needed, as sedatives/hypnotics. Hypnotic agents should be administered no more than once nightly and should not be used in combination.

Medications used for the as-needed treatment of anxiety/agitation and insomnia (eg, lorazepam and zolpidem) should not be used in close temporal proximity (defined as administration within 2 hours of each other). When lorazepam or zolpidem or other specified medications are not available, another similar agent at equivalent doses will be permitted as specified by the Medical Monitor. Opiates may be allowed in rare cases for a limited period of time with prior authorization from the Medical Monitor. Subjects who require treatment with one or more of the medications listed in Section 22, Appendix IV or Section 23, Appendix V should be excluded or discontinued (as appropriate) from the study. Since these lists of drugs are not comprehensive, Investigators should use medical judgment when a subject presents with a medication not on the list or consult with the Medical Monitor for clarification.

9.5.4. Prohibited Medications

In accordance with the approved product labeling for Latuda (see approved product labeling), lurasidone should not be used concomitantly with a strong CYP3A4 inhibitor (eg, ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil). Lurasidone should not be used concomitantly with a strong CYP3A4 inducer (eg, rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine). A list of strong CYP3A4 inhibitors and inducers included in Section 23, Appendix V).

The use of herbal supplements or other complementary or alternative medications during the trial is not permitted.

9.6. Contraception Requirements

Female Subjects

1. Female subject must be using and willing to continue using a highly effective form of birth control for at least 28 days prior to administration of the first dose of study drug, during the treatment period, and 2 months (60 days) after completion or premature discontinuation from the study drug. Highly effective forms of contraception include:
    - Combined estrogen and progestogen containing hormonal contraception (oral, intravaginal or transdermal) associated with inhibition of ovulation.
    - Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation.
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Bilateral tubal occlusion.
    - Bilateral tubal ligation.

- Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Women using hormonal contraception must use an additional form of contraception (eg, condom with spermicide).

2. A female subject is eligible to enter and participate in the study if she is of:
   a. Non-childbearing potential (ie, physiologically incapable of becoming pregnant, including any female who is pre-menarchal or post-menopausal);
      – Postmenopausal females defined as being amenorrheic for greater than 2 years (or confirmed by FSH level) with an appropriate clinical profile.
      – Women who have not been confirmed as postmenopausal should be advised to use contraception as outlined below.
      – Women who have had a hysterectomy, bilateral oophorectomy or bilateral salpingectomy (as determined by subject's medical history).
   b. Child-bearing potential (all females ≤ 65 years of age), has a negative pregnancy test at screening and agrees to satisfy one of the following requirements:
      – Complete abstinence from intercourse (as part of an abstinent lifestyle) a minimum of 2 months prior to administration of the first dose of study drug, throughout the Treatment Period, and for a minimum of 3 months after completion or premature discontinuation from the study drug; or,
      – Established use of highly effective methods of contraception from 1 month prior to administration of the first dose of study drug, during the Treatment Period, and 2 months after completion or premature discontinuation from the study drug. Highly effective methods of birth control are listed above in number 1).

Because of the unacceptable failure rate of barrier (chemical and/or physical) methods, the barrier method of contraception must only be used in combination with a highly effective method. Post-coital methods of contraception are not permitted.

Male Subjects

Male subject with female partner(s) of childbearing potential must ensure that his partner(s) uses the methods of contraception as outlined for female subjects above.

9.7. Guidance for Overdose

Refer to the approved product labeling for guidance for overdose with lurasidone oral tablets.

Overdose has not been evaluated for lurasidone injectable suspension.

9.8. Dietary Restrictions

Subjects will fast for at least 8 hours before dosing on Day -7 and Day -6. Subjects will fast for 4 hours after dosing on Day -7 and Day -6.

On Days -7 and -6, standard breakfast (minimum 350 calories) will be served 30 minutes prior to the planned dosing time.

Dosing of lurasidone 80 mg orally will take place 30 minutes after the start of breakfast. Subjects will receive dose administration at approximately the same time on each day of dosing during the study.

Lurasidone 80 mg will be administered with approximately 240-mL water on Days -7 and -6.

Water intake is restricted for one hour before and two hours after dose administration; after which water will be allowed ad libitum.

Lunch will be provided ≥ 4 hours postdose on Days -7, -6 and 1. Standard meals will be provided during the inpatient periods and outpatient clinic return visits when applicable.

10. STUDY ASSESSMENTS

A study schematic is presented in Figure 1. A summary of assessments to be conducted at each visit is presented in Table 2.

Assessments will be conducted within the time frames specified. All times are relative to the time of dosing for individual subjects unless otherwise specified. If no time window is specified, assessments should occur ± 1 hour of schedule.

10.1. Demographics and Baseline Characteristics

Subject self-report will be acceptable for listing all prior and concomitant medication use, demographics, medical history, psychiatric history, and evaluation for inclusion/exclusion except where specific protocol procedures are mandated to ensure appropriate enrollment (eg, certain baseline laboratory values). All medications taken within the 30 days before screening will be recorded.

Demographics (date of birth, sex, ethnicity, race), prior and current medications, and medical and psychiatric history will be collected.

10.2. Safety Assessments

The Investigator or appropriate designee will review results of safety assessments as they become available. The Sponsor must be kept fully informed of any clinically significant findings either at Screening or subsequently during study conduct through appropriate adverse event reporting and/or escalation to the Medical Monitor. Please also refer to the dose escalation stopping criteria Section 9.3).

10.2.1. 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).

Subjects should be queried in a non-leading manner, without specific prompting (eg, "Has there been any change in your health status since your last visit?"). See Section 11, Safety Reporting.

AEs and SAEs will be monitored throughout the study at all visits.

10.2.2. Clinical Laboratory Tests

The clinical laboratory tests required by protocol are listed in Section 20, Appendix II.

Blood and urine samples will be collected for clinical laboratory tests. All clinical laboratory tests will be performed locally. For clinical laboratory procedures, sampling, and shipping, the site will follow their standard procedures. All clinical laboratories will be College of American Pathologists and Clinical Laboratory Improvement Amendments (CLIA) (or equivalent) certified.

Any point of care kits that are performed on site by study personnel rather than in a lab must be CLIA waived and the study center must possess a CLIA certificate of Waiver.

A window of ± 10 minutes is allowed for clinical laboratory test sample collection. Samples will be obtained at the same time that other blood and urine samples are taken whenever possible.

Serum Prolactin levels will be blinded, except at screening and Day 1. Investigator will be notified if prolactin concentrations are > 200 ng/mL

10.2.3. Physical Examinations

Complete physical examinations will be performed. Worsening or changes in findings will be recorded as pretreatment events (prior to dosing) or as adverse events (after dosing).

10.2.4. Injection Site Assessments

10.2.4.1. Investigator Injection Site Assessments

The Investigator will assess the injection site using a rating of 1-4 on each of the 4 items (pain, tenderness, erythema/redness, and induration/swelling). A window of +1 minute is allowed for the immediately after injection timepoint, and a window of ± 5 minutes is allowed for the 6 and 12 hour injection site assessments on Day 1.

In addition subjects will be monitored for potential allergic reaction for 15 minutes after injection. A window of 0-5 minutes is allowed for this assessment.

10.2.4.2. Subject Injection Site Assessments

The subject will assess their injection site pain using a rating of 1-10 on a Likert scale (0 = no pain, 10 = worst pain). This will be completed prior to the Investigator's injection site

assessment. A window of +1 minute is allowed for the immediately after injection timepoint, and a window of ± 5 minutes is allowed for the 6 and 12 hour injection site assessments on Day 1.

10.2.5. Weight, Body Mass Index, and Height

Weight and height should be measured in street clothing with no shoes. Body mass index (BMI) will be calculated by the site (see Section 24, Appendix VI for calculation and BMI table).

10.2.6. Vital Signs

Blood pressure (supine and standing), pulse rate (supine and standing), respiration rate, and body temperature will be measured.

Supine blood pressure and pulse rate will be collected at the same time as 12-lead ECG (when 12-lead ECG is collected for the same timepoint). A window of ± 10 minutes of scheduled time is allowed. After Cohort 1, scheduled timepoints for vital signs measurements may be changed based on observed t_{max} of Lurasidone injectable suspension and its metabolites.

After lying supine for ≥ 5 minutes, systolic and diastolic blood pressures, respiratory rate, pulse rate, and oral temperature will be collected. Blood pressure and pulse rate will be taken again after standing for 2 to 4 minutes. The same arm should be used during each assessment of blood pressure and pulse rate throughout the study.

If a subject develops symptoms consistent with orthostatic hypotension (light-headedness, dizziness, or changes in sensorium upon standing) at any point, his or her supine and standing blood pressure and pulse rate should be collected at that time in the manner described above. Vital signs will be obtained prior to clinical laboratory collection and performance of an ECG.

10.2.7. 12-Lead ECG

All ECGs will be obtained in the supine position, after the subject has been resting supine for at least 5 minutes. ECGs will be 12-lead with a 10-second rhythm strip. ECGs should be obtained prior to drawing blood samples. All attempts should be made to use the same ECG recorder for all visits within individual subjects. ECGs will be centrally read at a core lab according to established quality assurance procedures for inter/intra reader variability. Refer to Section 19, Appendix I for additional information.

A window of ± 15 minutes of scheduled time is allowed. After Cohort 1, scheduled timepoints may be changed based on observed t_{max} of Lurasidone injectable suspension and its metabolites.

10.2.8. Columbia-Suicidality 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. The C-SSRS will be administered by a trained rater at the site.

This study will utilize 2 versions of the C-SSRS. At the Screening visit, the Screening/Baseline version will be completed; for all subsequent visits, the “Since Last Visit” version of the C-SSRS will be administered.

Subjects who answer "yes" to "suicidal ideation" item 4 (active suicidal ideation with some intent to act, without specific plan) or item 5 (active suicidal ideation with specific plan and intent) on the C-SSRS assessment at Screening (in the past 1 month) are not eligible and must be referred to the Investigator for follow-up evaluation.

Further information regarding administration of the C-SSRS, including rater training and certification as well as recording C-SSRS scores, will be provided in the Study Reference Manual.

10.3. Pharmacokinetic Assessments

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.

Validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods will be used for determination of lurasidone and metabolite concentrations.

The detailed sample collection procedures are provided in Section 21, Appendix III for blood and urine sampling and sample handling guidelines. Blood and urine collection date and times (clock time) must be recorded.

A window of ± 5 minutes of scheduled time (up to 8 hours postdose), and ± 10 minutes of scheduled time (from 12 hours postdose onward) is allowed. Blood sampling timepoints for PK assessment for subsequent cohorts may be modified based on serum concentration data from initial cohort(s). Evaluation of the relationship between the timing of below limit of quantification (BLQ) and the elimination half-life will be used to justify the revised blood sampling for PK and safety assessment schedule.

For subjects receiving lurasidone injectable suspension treatments, all samples will be measured for lurasidone and its metabolites 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. For placebo subjects usually only a subset of serum and urine samples will be measured to confirm no dosing error, interference, or occurrence of contamination.

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

Dose proportionality of Lurasidone injectable suspension will be assessed using a power model for C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ of Lurasidone injectable suspension with a formula of ln (PK parameter) = $\alpha + \beta \cdot \ln$ (dose level).

The following PK parameters, determined by noncompartmental methods using Phoenix® WinNonlin® version 6.4 or higher, are based on the individual subject's serum concentration data.

Serum Parameters

C_{max} Maximum observed serum concentration

t_{max} Time of occurrence of serum C_{max}

C_{last} The last postdose quantifiable serum concentration

t_{last} Time of the last postdose quantifiable serum concentration

λ_z Elimination rate constant obtained from a linear regression of the natural log (ln) transformed concentrations versus time data in terminal phase. A minimum of 3 points, clearly visible in the terminal phase, are required to calculate λ_z.

$t_{½}$ Terminal elimination half-life, calculated as ln(2)/ λ_z.

$AUC_{0\text{-last}}$ Area under the analyte concentration-time curve from time 0 ($t_0 = 0$) to the last postdose quantifiable serum concentration calculated using the linear up log down trapezoidal method.

$$AUC_{0-last} = \sum_{i=1}^{k} \left(\frac{C_{i-1} + C_i}{2}\right)(t_i - t_{i-1}),$$

where C_i is the drug concentration at time t_i, i = 1, 2, …, k.

$AUC_{0\text{-}\infty}$ Area under the analyte concentration-time curve from 0 to infinity calculated by summing $AUC_{0\text{-last}}$ and the AUC extrapolated from t_{last} to infinity.

$$AUC_{0-\infty} = AUC_{0-last} + \frac{C_{last}}{|\lambda_z|}.$$

If $C_{last} / |\lambda_z|$ is greater than 30% of $AUC_{0\text{-}\infty}$, then $AUC_{0\text{-}\infty}$ was considered missing.

CL/F Apparent clearance calculated as Dose/$AUC_{0\text{-}\infty}$

V_z/F Apparent volume of distribution calculated as Dose/$AUC_{0\text{-}\infty}/\lambda_z$

MRC_{max} 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}

$MRAUC_{0\text{-}\infty}$ The ratio of metabolites (ID-14283, ID-14326, ID-11614, ID-20219, and ID-20220) $AUC_{0\text{-}\infty}$ (mAUC) to parent (lurasidone injectable suspension) $AUC_{0\text{-}\infty}$ (pAUC) calculated as: mAUC divided by pAUC

Urine Parameters

$Ae_{0\text{-}144h}$ The cumulative amount of the analyte excreted from time zero to 144 hours. The amount of the analyte excreted in the urine during a given collection interval is calculated as the product of the urinary volume and the urinary concentration. The cumulative amount of the analyte excreted during the time interval is calculated by summing the amounts excreted in all of the collection intervals between t1 and t2; nominal t1 holds the value 0 and nominal t2 holds the value 144, respectively.

CL_R Renal clearance for an analyte during the time interval t1 and t2 is calculated as:

$$CL_R = Ae_{t1\text{-}t2}/AUC_{t1\text{-}t2}$$

Fe Percent of administered analyte excreted unchanged in urine during the time interval t1 to t2 is calculated as:

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

Remaining serum samples after PK analysis may also be used for the additional characterization and/or bioanalytical method development of putative metabolites of lurasidone injectable suspension and for other exploratory measurements, if needed.

10.4. Pharmacodynamic Assessment (PANSS)

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.

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

10.5. Study Visits and Assessments

10.5.1. Days -35 to -13 (Screening)

Subjects will be evaluated during the Screening period to determine their eligibility to enroll in the study.

To determine subject eligibility, abnormal Screening clinical laboratory tests may only be repeated after discussion with the Medical Monitor.

To determine subject eligibility, Screening ECG may only be repeated due to technical issues.

The following study-related procedures will be performed at Screening:

- Obtain Informed Consent.
- Review Inclusion/Exclusion Criteria.

- Record Medical and Psychiatric History.
- Record Demographics.
- Perform Physical Examination.
- Record Height.
- Record Weight and BMI.
- Obtain Vital Signs.
- Perform 12-Lead ECG.
- Collect Blood and Urine Samples for Clinical Laboratory Tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Lipid Panel
  - Thyroid Panel
  - Coagulation Panel
- Collect Blood Sample for Serum Prolactin.
- Collect Blood Sample for Serology.
- Collect Blood Sample for b-hCG Serum Pregnancy Test (female subjects).
- Collect Urine Sample for:
  - Urine Drug Screen
  - Urine Alcohol Test
- Administer C-SSRS (Screening/Baseline Version).
- Administer PANSS.
- Record Prior and Concomitant Medications.
- Record Pretreatment Events.
- Schedule Next Visit.

10.5.2. Washout/Taper Period: Days -12 to -8

Subjects are required to be inpatient for the washout/taper period. Subjects will be admitted to the clinical site on Day -12. Subjects may be admitted earlier, depending on the required washout for their current antipsychotic medications (ie, 5 to 6 half-lives prior to Day -8).

10.5.2.1. Day -12 (Washout/Taper)

The following study-related procedures will be performed:

- Admit Subject to Clinical Site.
- Perform Physical Examination.
- Obtain Vital Signs.
- Perform 12-Lead ECG.
- Collect Blood Sample for b-hCG Serum Pregnancy Test (female subjects).
- Collect Urine Sample for:
  - Urine Drug Screen
  - Urine Alcohol Test
- Begin washout/taper of psychotropic medications (may begin Day -19).
- Provide Meals.
- Record Concomitant Medications.
- Record Pretreatment Events.

10.5.2.2. Days -11 to -9 (Washout/Taper)

The following study related procedures will be performed:

- Awaken Subject.
- Provide Meals.
- Record Concomitant Medications.
- Record Pretreatment Events.

10.5.2.3. Day -8 (End of Washout/Taper Period)

The following study related procedures will be performed:

- Awaken Subject.
- Provide Meals.
- Review Inclusion/Exclusion Criteria.
- Perform Physical Examination.
- Record Weight and BMI.
- Obtain Vital Signs.
- Perform 12-Lead ECG.
- Collect Blood and Urine Samples for Clinical Laboratory Tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis

  - Lipid Panel
  - Thyroid Panel
  - Coagulation Panel
- Collect Blood Sample for Serum Prolactin.
- Collect Blood Sample for b-hCG Serum Pregnancy Test (female subjects).
- Collect Urine Sample for:
  - Urine Drug Screen
  - Urine Alcohol Test
- Administer C-SSRS (Since Last Visit version; pre-oral dose assessment).
- Record Concomitant Medications.
- Record Pretreatment Events.
- Subjects will fast for 8 hours before receiving study drug on Day -7.

10.5.3. Treatment/Observation Period, Days -7 to 28

Subjects are required to be inpatient until at least Day 15.

Dosing with oral lurasidone tablets to ensure subjects are able to tolerate treatment with lurasidone will occur on Day -7 and Day -6 (single oral lurasidone 80 mg dose each day).

Safety monitoring and washout of oral lurasidone will occur until Day -1.

Subjects who tolerate oral lurasidone will be randomized on Day 1 to either lurasidone or placebo injection. Safety monitoring and observation (including assessment of the injection site) as well as PK and pharmacodynamic assessments during the inpatient period will occur from Day 1 through Day 15.

Subjects may be discharged on Day 15 if in the Investigator's opinion the subject is clinically stable.

Subjects may remain inpatient at the Investigator's discretion up to Day 33.

10.5.3.1. Day -7 (Oral Lurasidone Dosing)

<u>The following study related procedures will be performed predose:</u>

- Awaken Subject.
- Provide breakfast (350 calories).
- Obtain Vital Signs.
- Perform 12-Lead ECG.
- Collect Blood Sample for PK.
- Administer PANSS.

- Dispense Oral Lurasidone and Observe Subject Administer Dose.
- Record Concomitant Medications.
- Record Adverse Events.

The following study related procedures will be performed 2 hours postdose:

- Obtain Vital Signs.
- Perform 12-Lead ECG.
- Collect Blood Sample for PK.
- Administer C-SSRS (Since Last Visit version).
- Record Concomitant Medications.
- Record Adverse Events.
- Subjects will fast for 4 hours postdose.
- Subjects will fast for 8 hours before receiving study drug on Day -6.

10.5.3.2. Day -6 (Oral Lurasidone Dosing)

The following study related procedures will be performed predose:

- Awaken Subject.
- Provide breakfast (350 calories).
- Obtain Vital Signs (time-matched to predose on Day -7).
- Perform 12-Lead ECG (time-matched to predose on Day -7).
- Collect Blood Sample for PK.
- Dispense Oral Lurasidone and Observe Subject Administer Dose.
- Record Concomitant Medications.
- Record Adverse Events.

The following study related procedures will be performed 2 hours postdose:

- Obtain Vital Signs.
- Perform 12-Lead ECG.
- Record Concomitant Medications.
- Record Adverse Events.
- Subjects will fast for 4 hours postdose.

10.5.3.3. Days -5 to -1 (Safety and Tolerability Observation)

The following study related procedures will be performed:

- Awaken Subject (daily).

- Provide Meals (daily).
- Obtain Vital Signs on Day -1 (time-matched to predose on Day -7).
- Administer C-SSRS on Day -1 (Since Last Visit version; pre-injection dose assessment).
- Record Concomitant Medications.
- Record Adverse Events.

10.5.3.4. Day 1 (Baseline/Randomization and Lurasidone or Placebo Injection Dosing)

The following study related procedures will be performed predose:

- Awaken Subject.
- Provide Meals.
- Obtain Vital Signs.
- Perform 12-Lead ECG.
- Collect Blood and Urine Samples for Clinical Laboratory Tests (time-matched to Predose on Day -7):
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Lipid Panel
  - Thyroid Panel
  - Coagulation Panel
- Collect Blood Sample for Serum Prolactin.
- Collect Blood Sample for PK (predose).
- Collect Urine Sample for PK (-0.5 to 0 hours predose).
- Administer PANSS.
- Randomize Subject.
- Dispense Lurasidone or Placebo Injection.
- Administer Lurasidone or Placebo Injection.
- Record Concomitant Medications.
- Record Adverse Events.

The following study related procedures will be performed postdose:

- Subject Injection Site Pain Assessment immediately postdose, and 6 hours and 12 hours postdose. A window of +1 minute is allowed for the immediately after

injection timepoint, and a window of ± 5 minutes is allowed for the 6 and 12 hour timepoints.

- Investigator Injection Site Safety Assessment immediately postdose, and 6 hours and 12 hours postdose. A window of +1 minute is allowed for the immediately after injection timepoint, and a window of ± 5 minutes is allowed for the 6 and 12 hour timepoints. In addition subjects will be monitored for potential allergic reaction for 15 minutes after injection. A window of 0-5 minutes is allowed for this assessment.
- Obtain Vital Signs at 6 and 12 hours postdose.
- Perform 12-lead ECG at 6 and 12 hours postdose.
- Collect Blood Sample for PK at 2, 4, 6, 12 hours postdose.
- Collect Urine Sample for PK at 0 to 24 hours postdose.
- Administer C-SSRS (Since Last Visit version) at 12 hours postdose.
- Record Concomitant Medications.
- Record Adverse Events.

10.5.3.5. Days 2 to 8 (Safety and Tolerability Observation)

The following study related procedures will be performed:

- Awaken Subject (daily).
- Provide Meals (daily).
- Subject Injection Site Pain Assessment on Days 2 and 8.
- Investigator Injection Site Safety Assessment (daily).
- Obtain Vital Signs on Days 3, 5, and 7(time-matched to the injection predose timepoint on Day 1).
- Perform 12-Lead ECG on Days 3, 5, and 7 (time-matched to the injection predose timepoint on Day 1).
- Collect Blood and Urine Samples for Clinical Laboratory Tests on Day 8 (time-matched to the injection predose timepoint on Day 1):
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Obtain Blood Sample for Serum Prolactin (Day 8).
- Collect Blood Sample for PK at 24, 48, 72, 96, 120 and 144 hours post-injection dose.
- Collect Urine Sample for PK at 24 to 48, 48 to 72, 72 to 96, 96 to 120, and 120 to 144 hours post-injection dose.
- Administer C-SSRS on Day 7.

- Administer PANSS on Day 8.
- Record Concomitant Medications (daily).
- Record Adverse Events (daily).

10.5.3.6. Days 9 to 14 (Safety and Tolerability Observation)

The following study related procedures will be performed:

- Awaken Subject (daily).
- Provide Meals (daily).
- Investigator Injection Site Assessment (daily).
- Obtain Vital Signs on Days 9, 11, and 13 (time-matched to the injection predose timepoint on Day 1)
- Perform 12-Lead ECG on Days 9, 11, and 13 (time-matched to the injection predose timepoint on Day 1).
- Record Concomitant Medications (daily).
- Record Adverse Events (daily).

10.5.3.7. Day 15 (Safety and Tolerability Observation)

- Awaken Subject.
- Provide Meals.
- Subject Injection Site Pain Assessment.
- Investigator Injection Site Safety Assessment.
- Perform Physical Examination.
- Obtain Vital Signs (time-matched to the injection predose timepoint on Day 1).
- Perform 12-Lead ECG (time-matched to the injection predose timepoint on Day 1.
- Collect Blood and Urine Samples for Clinical Laboratory Tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Lipid Panel
  - Thyroid Panel
  - Coagulation Panel
- Collect Blood Sample for Serum Prolactin.
- Blood Sampling for Serum PK.

- Administer C-SSRS (Since Last Visit version).
- Administer PANSS.
- Record Concomitant Medications.
- Record Adverse Events.
- Schedule Next Visit.
- Discharge Subject (if subject is clinically stable in the Investigator's opinion).

10.5.3.8. Day 22 (Safety and Tolerability Observation)

Subjects may remain inpatient at the Investigator's discretion throughout the Treatment and Observation Period.

Subjects who have been discharged on Day 15 will have a clinic visit on Day 22.

The following study related procedures will be performed:

- Awaken Subject (daily if inpatient).
- Provide Meals (daily if inpatient).
- Obtain Vital Signs on Day 22 (approximately time-matched to the injection predose timepoint on Day 1).
- Perform 12-Lead ECG on Day 22 (approximately time-matched to the injection predose timepoint on Day 1).
- Collect Blood and Urine Samples for Clinical Laboratory Tests on Day 22 (time-matched to the injection predose timepoint on Day 1):
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Obtain Blood Sample for Serum Prolactin on Day 22.
- Obtain Blood Sample for PK On Day 22.
- Administer C-SSRS on Day 22.
- Administer PANSS on Day 22.
- Schedule Next Visit.
- Discharge Subject (if clinically stable in the Investigator's opinion).
- Subject Injection Site Pain Assessment on Day 22.
- Investigator Injection Site Safety Assessment on Day 22.
- Record Concomitant Medications.
- Record Adverse Events.

10.5.4. Days 29 to 33 (End of Safety and Tolerability Observation and Beginning of Restabilization)

Subjects are required to be inpatient Days 29 to 33. Day 29 is the end of the safety and tolerability observation period for lurasidone injectable suspension/placebo injection. Day 29 is also the start of the restabilization period.

Restabilization' refers to the reintroduction of each subject's prior medications that were taken prior to entry into the study including their psychotropic medications. For early termination patients who received lurasidone dosing, following follow-up procedures they will need to be restabilized following the restabilization procedures.

Subjects who discontinue the study prior to Day 29 will undergo assessments scheduled for Day 29 at the time of discontinuation.

10.5.4.1. Day 29 (End of Safety and Tolerability Observation and Beginning of Restabilization)

- Awaken subject (if inpatient).
- Provide meals (if inpatient).
- Admit subject to clinic (if previously discharged).
- Perform Physical Examination.
- Record Weight and BMI.
- Obtain Vital Signs (approximately time matched to the injection predose timepoint on Day 1).
- Perform 12-Lead ECG (approximately time matched to the injection predose timepoint on Day 1).
- Collect Blood and Urine Samples for Clinical Laboratory Tests on (time matched to the injection predose timepoint on Day 1):
  - Hematology
  - Serum Chemistry
  - Urinalysis
  - Lipid Panel
  - Coagulation Panel
  - Thyroid Panel
- Obtain Blood Sample for Serum Prolactin.
- Obtain Blood Sample for PK.
- Obtain Blood Sample for b-hCG Serum Pregnancy Test (female subjects).
- Obtain Urine Sample for Urine Drug Screen and Urine Alcohol Test.
- Administer C-SSRS (Since Last Visit version).

- Administer PANSS.
- Subject Injection Site Pain Assessment.
- Investigator Injection Site Safety Assessment.
- Record Concomitant Medications.
- Reintroduce prior psychotropic medications.
- Record Adverse Events.

10.5.4.2. Days 30-32 (Restabilization)

The following procedures will be performed:

- Awaken Subject.
- Provide Meals.
- Continue prior psychotropic medications.
- Record Concomitant Medications.
- Record Adverse Events.

10.5.4.3. Day 33 (End of Restabilization)

The following study-related procedures will be performed:

- Awaken Subject.
- Provide Meals.
- Perform Physical Examination.
- Record Weight and BMI.
- Obtain Vital Signs (approximately time-matched to the injection predose timepoint on Day 1).
- Perform 12-Lead ECG (approximately time-matched to the injection predose timepoint on Day 1).
- Collect Blood and Urine Samples for Clinical Laboratory Tests (time-matched to the injection predose timepoint on Day 1):
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Collect Blood Sample for Serum Prolactin.
- Administer C-SSRS (Since Last Visit version).
- Continue prior psychotropic medications.
- Record Concomitant Medications.

- Record Adverse Events.
- Schedule Next Visit.
- Discharge Subject.

10.5.5. Follow-up/Study Completion, Day 61 ± 2

All subjects will have an outpatient follow-up safety visit.

Subjects who discontinue the study after Day 29 but prior to Day 61 will undergo assessments scheduled for Day 61 at the time of discontinuation.

The following study-related procedures will be performed:

- Perform Physical Examination.
- Record Weight and BMI.
- Obtain Vital Signs.
- Perform 12-Lead ECG.
- Collect Blood and Urine Samples for Clinical Laboratory Tests:
  - Hematology
  - Serum Chemistry
  - Urinalysis
- Collect Blood Sample for Serum Prolactin.
- Collect Blood Sample for PK.
- Administer C-SSRS (Since Last Visit version).
- Record Concomitant Medications.
- Record Adverse Events.

11. SAFETY REPORTING

11.1. Definitions

11.1.1. Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Untoward medical occurrences that occur between the time of signing the informed consent form (ICF) and drug administration are pre-treatment events. Those that occur after administration of study drug are considered AEs. Pre-treatment hospitalizations that occur in accordance with local clinical practice during the screening period (for wash-out from prior or concomitant medications) will not be considered as SAEs and do not need to be reported as such. Any untoward event that may occur during the hospitalization must be recorded as a pretreatment event. If hospitalization is prolonged by an untoward event, the event must be reported as an SAE.

An AE can, therefore, be any unfavorable and unintended sign (including an abnormal or clinically significant laboratory finding), symptom, or disease occurring after the administration of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. AEs may include the onset of new illness and the exacerbation of pre-existing conditions.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms.

11.1.2. Serious Adverse Events

A serious adverse event (SAE) is pretreatment event or an AE that meets one or more of the following criteria:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the subject or may require a medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

The term “severe” is often used to describe the severity of a specific event (as in mild, moderate, or severe myocardial infarction) (see Section 11.3); the event itself, however, may be of

relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning as defined by the criteria above.

During the study, if a subject has a hospitalization or procedure (eg, elective surgery) that was scheduled before the study entry, ie, before informed consent for an event/condition that occurred before the study, the hospitalization is considered a therapeutic intervention and not the result of a SAE. However, if the event/condition worsens during the study, it should be reported as an AE (or SAE, if the event/condition results in a serious outcome such as prolongation of hospitalization).

Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. This definition does not include an event that had it occurred in a more severe form might have caused death.

SAE criteria information will be captured on the CRF.

11.2. Objective Findings

Clinically significant abnormal objective findings (eg, clinical laboratory value, ECG value, and physical examination observation) will also be recorded as AEs.

When a clear diagnosis is available that explains the objective findings, this diagnosis will be recorded as the AE, and not the abnormal objective finding (eg, viral hepatitis will be recorded as the AE, not transaminase elevation). If a definite diagnosis is not available, then the sign (eg, clinically significant elevation of transaminase levels) or symptom (eg, abdominal pain) will be recorded as the AE.

Clinical laboratory test results will be reviewed by the Investigator. The Investigator must determine the clinical significance of all out of range values. Clinical laboratory test with possibly drug-related or clinically relevant abnormal values of uncertain causality may be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

Clinical Laboratory Tests Outside the Normal Range: Any value outside the normal range will be flagged for the attention of the Investigator or appropriate designee at the study center. The Investigator or appropriate designee will indicate whether or not the value is of clinical significance. If the result of any test (or repeat test, if done) from the samples taken during Screening is indicated as clinically significant and is not covered by the inclusion criteria in Section 7.1, the subject will not be allowed into the study. Additional testing during the study may be done if medically indicated. If a clinically significant abnormality is found in the samples taken after dosing, during the study, and/or at the Follow-Up/Study Completion Visit, this should be recorded as an AE and the subject will be followed until the test(s) has (have) normalized or stabilized.

All on-site ECG tracings and ECG over-read reports will be reviewed by the Investigator. The Investigator must determine the clinical significance of all abnormal ECGs. ECG with possibly drug-related or clinically relevant abnormal findings of uncertain causality may be repeated. Any abnormal ECGs that persist should be followed at the discretion of the Investigator. ECG tracings will be initialed and dated on all pages by the Investigator.

11.3. Collection and Recording of Adverse Events

All pre-treatment events and AEs must be recorded in the subject's study records/source documents in accordance with the Investigator's normal clinical practice.

All pre-treatment events and AEs must be recorded on the CRF.

Pre-treatment events will be recorded from the time informed consent is provided at Screening until just prior to first lurasidone oral tablet study drug dose at Day -7. AEs will be recorded beginning after first study drug dose administration on Day 1 until the follow-up/study completion visit at Day 61 (± 2).

All AEs will be followed until resolution, stabilization of the condition, the event is otherwise explained, or the subject is lost to follow-up.

Each AE is to be evaluated for duration, severity, frequency, seriousness, action taken with the study treatment, outcome, and causal relationship to the study treatment. Definitions for severity, frequency, action taken with the study treatment, outcome, and causal relationship to the study treatment are presented below.

The severity of AE:

- **Mild** – Ordinarily transient symptoms that do not influence performance of subject's daily activities. Other treatment is not ordinarily indicated.
- **Moderate** – Marked symptoms sufficient to make the subject uncomfortable. Moderate influence on performance of subject's daily activities. Other treatment may be necessary.
- **Severe** – Symptoms cause considerable discomfort. Substantial influence on subject's daily activities. May be unable to continue the study, and other treatment may be necessary.

The frequency of AE:

- **Once** – an isolated episode.
- **Intermittent** – occurs on two or more separate occasions.
- **Continuous** – does not abate from date of onset to date of resolution.

The outcome of the AE:

- **Recovered/Resolved**
- **Recovering/Resolving**
- **Not Recovered/Not Resolved**
- **Recovered/Resolved with Sequelae**
- **Fatal**
- **Unknown**

The causal relationship of the AE to the study treatment:

- **Not related**

- **Not related** – Improbable temporal relationship and is plausibly related to other drugs or underlying disease.

- **Related**
  - **Possible** – occurred in a reasonable time after study drug administration, but could be related to concurrent drugs or underlying disease.
  - **Probable** – occurred in a reasonable time after study drug administration, is unlikely to be attributable to concurrent drugs or underlying disease, and there is a plausible mechanism to implicate the study drug.
  - **Definite** – occurred in a reasonable time after study drug administration and cannot be explained by concurrent drugs or underlying disease. The AE should respond to dechallenge/rechallenge, however, this is not mandatory before assigning a definite causality.

The Medical Advisor is the initial contact person for protocol related questions or discussion of AEs. The contact information for the Medical Advisor as well as other emergency contact information can be found in Table 1 of this protocol.

11.4. Immediately Reportable Events

The following medical events must be immediately reported to the Sponsor:

- SAE
- Pregnancy

Emergency contact information can be found in Table 1.

11.4.1. Serious Adverse Event

If the Investigator or study center staff becomes aware of an SAE that occurs in a study subject up to and including the final follow-up, this must be reported immediately to the Sponsor whether considered related or unrelated to the study drug. SAEs must be recorded on the CRF and the data recorded should agree with that on the SAE form.

Following the end of subject participation in the study, the Investigator or an authorized delegate should report SAEs "spontaneously" to the Sponsor PPD Pharmacovigilance (PVG) if considered at least possibly related to the study drug.

SAEs will be followed until resolution, loss to follow-up, stabilization of condition, or the event is otherwise explained.

In addition to the initial telephone notification, an initial SAE form as applicable must be completed and signed and sent via fax or email (see Table 1) to the Sponsor PPD-PVG within 24 hours of the Investigator or study center staff becoming aware of the event. The SAE form must be signed by the Investigator or appropriate designee. The Sponsor PPD-PVG provides the SAE form used to report SAEs.

SAEs must be promptly reported to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) by the Principal Investigator or the appropriate person at the study center if required per IRB/IEC guidelines.

The appropriate PVG group must be contacted immediately upon first knowledge of the incident. The immediate report should be made by the Investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE or pregnancy.

11.4.2. Pregnancy

Pregnancies that occur from the time that informed consent is signed through the final follow-up/study completion visit will be collected and reported on the Pregnancy Event Form.

If a subject becomes pregnant during the course of the study, she will be instructed to return promptly/within 48 hours of the first notification of pregnancy to the study center and undergo a serum/urine pregnancy test, as confirmation of pregnancy. Every effort will be made to follow up all pregnancies, including those in the female partner of male subjects, until resolution (ie, termination [voluntary or spontaneous] or birth), providing the volunteers consent to follow-up.

To report a pregnancy, the Pregnancy Event Form must be completed and sent via fax to PPD-PVG within 24 hours of the Investigator or study center staff becoming aware of the pregnancy The Sponsor provides the Pregnancy Event Form.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication or other AEs were detected.

12. TERMINATION OF SUBJECT FROM STUDY/DISCONTINUATION OF STUDY DRUG

12.1. Criteria for Subject Termination

Subjects may terminate the study participation at any time for any reason.

The possible reasons for the termination of study participation are as follows:

- Adverse event.
- Lost to follow-up (specify).
- Pregnancy.
- Withdrawal by subject (specify).
- Protocol deviation (specify).
- Death.
- Other (specify).

If at any time during the course of the study, in the opinion of the Investigator, the subject may no longer safely participate due to a change in medical status (eg, experiences an AE, becomes pregnant), the subject must be discontinued from the study.

The reason for discontinuation and information on the epoch will be recorded on the appropriate CRF. In case of death, the date of death should be captured on the CRF.

Alternate subjects may be admitted to the clinical site in order to ensure that 8 subjects are dosed in each cohort. Subjects who are randomized but not dosed will be replaced by the alternate subject(s).

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).

Subjects who discontinue the study prior to Day 29 will undergo assessments scheduled for Day 29 at the time of discontinuation (see Section 10.5.4.1). Subjects who discontinue the study after Day 29 but prior to Day 61 will undergo assessments scheduled for Day 61 at the time of discontinuation (see Section 10.5.5).

13. STUDY TERMINATION

The Sponsor reserves the right to discontinue the study at this study center for safety or administrative reasons at any time while safeguarding that early termination does not compromise subjects' safety or well-being. In particular, a study center that does not recruit at an acceptable rate may be closed. Should the study be terminated and/or the study center closed for whatever reason, all documentation and study medications pertaining to the study must be returned to the Sponsor or its representative.

If, in the opinion of the Investigator, clinical observations suggest it may be unsafe to continue, the Investigator may terminate part or the entire study after consultation with the Sponsor.

In the event of study or site termination, subjects will be required to undergo final study assessments scheduled for the Day 61 (± 2) visit at the time of discontinuation. After study completion, subjects will be provided with access to standard care.

14. STATISTICS

The comprehensive statistical analysis plan (SAP) will provide details on the statistical methods planned for this study and will be finalized prior to database lock.

14.1. 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.

14.2. Analysis Populations

Three analysis populations will be defined:

- Safety population: The Safety population will consist of all subjects who were randomized and received study drug. All analyses will be performed according to treatment received. This population will be used for analysis of baseline and safety data.
- Pharmacokinetic (PK) population: The PK population includes Safety population subjects who received lurasidone injectable suspension (active) and have at least 1 postdose quantifiable serum or urine lurasidone injectable suspension and metabolite(s) concentration. This population will be used for PK analysis.
- Pharmacodynamic (PD) population: The PD population will include all subjects in the Safety Population who have valid baseline and at least one post-baseline PANSS assessment.

14.3. Data Analysis

Descriptive summary statistics for continuous variables will include the number of subjects (n), mean, standard deviation (SD), median, minimum and maximum. Descriptive summary statistics for categorical variables will include frequency counts and percentages (n [%]). Subjects dosed with placebo will be analyzed as a pooled group. Descriptive summary statistics for PK parameters will also include coefficient of variation (CV%), geometric mean and geometric CV%.

SAS® Version 9.4 or higher will be used for all analyses.

14.3.1. Subject Disposition

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 treatment and dosed and not dosed, who were included in each population will 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 and overall.

14.3.2. Drug Exposure and Compliance

A data listing, by subject, containing the study medication dosing and dosing errors, if any, will be provided. Because this is a single dose study, treatment compliance will not be summarized.

14.3.3. Important Protocol Deviations

Important protocol deviations (IPDs) will be identified and documented based on a review of potentially IPDs. The potentially IPDs will be identified through programmatic checks of study data, as well as through review of selected data listings. The potentially IPDs to be reviewed include, but are not limited to, subjects who:

- Did not meet inclusion/exclusion criteria
- Received any disallowed concomitant medication
- Informed consent date obtained after date of study medication
- Other

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

14.3.4. Demographic and Baseline Characteristics

The number and percentage of subjects in each racial group will be summarized. Age, height, weight, and BMI may be summarized using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum).

The medical history of subjects will be coded by System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA v. 20.1 or higher). The number and percentage of subjects with abnormal findings in each SOC and each PT will be summarized.

14.3.5. Safety Analyses

14.3.5.1. Adverse Events

All AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher. AEs are untoward medical occurrences:

- that occurred on or after the study medication,
- with a missing start date and a stop date on or after the study medication, or
- with both a missing start and stop date.

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

The following AEs will be summarized and presented by treatment and by MedDRA SOC and PT for the Safety population:

- All AEs (including number of events and subject incidence).
- AEs by severity (mild, moderate, severe).
- AEs by relationship to the study treatment (related, or not related).

The following conventions will be followed in summarizing AEs:

- For subject incidence summaries, each subject will be counted only once within each SOC and within each preferred term.
- If a subject reports more than one AE within a preferred term and/or a system organ class, the AE with the highest known severity within each system organ class and within each preferred term will be included in the summaries by severity.
- For summaries by relationship to the study medication, AEs will be grouped as "related" or "not related," AEs with relationship to study medication assessed as "possible," "probable," or "definite" will be grouped as "related," and AEs with relationship to study medication assessed as "not related" will be summarized as "not related." If a subject reports more than one AE within the same treatment regimen, SOC and PT, and any are related, it will be summarized as related.

Summaries of SAEs and AEs leading to study discontinuation will be provided. Additional summaries may be provided using AEs of special interest.

A listing of all AEs, as well as a listing of deaths, a listing of SAEs, and a listing of AEs leading to study discontinuation will be provided.

14.3.5.2. Clinical Laboratory Assessments

All summaries involving clinical chemistry, hematology, and urinalysis tests will be based on the Safety population.

Descriptive statistics for observed value and change from baseline will be displayed at each visit by treatment for each chemistry, hematology, and urinalysis laboratory test measured on a continuous scale.

Serum prolactin values will be summarized by treatment and gender.

The normal reference ranges for laboratory tests will be used to determine whether the laboratory test value is below, within, or above the normal range. Shifts from baseline will be produced by treatment to show the percentage of subjects with laboratory test values below, within, and above the normal range.

The number and percentage of subjects with a Markedly Abnormal Post-baseline Laboratory value (MAPLV, to be defined in the SAP) for select parameters will be summarized by treatment.

The data listings for laboratory parameters will flag values outside of the reference range.

14.3.5.3. ECGs/Centrally-read ECG/Holter Monitor

Observed values, as well as change from baseline in ECG parameters will be summarized by treatment.

The number (percentage) of subjects with observed QTcF values > 450, > 480, and > 500 msec and increases in QTcF from baseline of > 30 and > 60 msec; increase in PR interval from baseline > 25% and a PR interval > 200 msec; increase in QRS interval from baseline > 25% and a QRS interval > 120 msec; decrease in HR from baseline > 25% and a HR < 50 bpm; and increase in HR from baseline > 25% and a HR > 100 bpm will be summarized by each treatment group, respectively.

Electrocardiogram clinical interpretation of ECG findings will be presented in data listings.

14.3.5.4. Vital Signs

Body temperature, respiration rate, pulse rate (supine and standing), blood pressure (supine and standing), and weight will be summarized using descriptive statistics at each time point by treatment group. Changes from baseline will be summarized in the same manner. The number and percentage of subjects with Sponsor defined markedly abnormal post-baseline vital sign values (MAPVS) will be presented by treatment.

The number and percentage of subjects with orthostatic hypotension and orthostatic tachycardia will be summarized by treatment. Orthostatic hypotension is defined as a decrease of ≥ 20 mmHg in systolic blood pressure or ≥ 10 mmHg in diastolic blood pressure after the subject had been standing for at least 2 to 4 minutes, 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 after the subject was standing for at least 2 to 4 minutes, compared to the pulse rate measured in the supine position.

14.3.5.5. Columbia-Suicide Severity Rating Scale (C-SSRS)

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.

14.3.5.6. Physical Examination

Findings from the physical examinations will be presented as follows: pre-existing clinically significant conditions recorded as medical history will be summarized, and new clinically significant conditions recorded as an AE will also be summarized.

14.3.5.7. Investigator Injection Site Safety Assessment and Subject Injection Site Pain Assessment

The investigator injection site safety assessment and subject injection site pain assessment will be summarized by treatment. Details will be provided in the SAP.

14.3.5.8. Concomitant Medications

All medications will be coded to indication-specific ATC (Anatomical Therapeutic Chemical) classification (ie, ATC level 3) and preferred term according to the World Health Organization Drug (WHODRUG) anatomical therapeutic chemical (ATC) classification level 3 and Preferred Term (PT) (2017 September 01 or more recent).

Any medications taken during the course of the study, with a start date on or after the date of the dose of study medication; or with a start date prior to, and an end date on or after, the date of the dose of study medication, or marked as ongoing, will be considered concomitant medications. Medications that ended prior to the date of the dose of study medication will be considered prior medications. The number and percentage of subjects using each prior and concomitant medication will be summarized by treatment group and by ATC level 3 and PT using the Safety population. Subjects with multiple uses of a medication will be counted only once for a given ATC or PT.

A detailed listing of prior and concomitant medications taken by subjects will be provided.

14.3.5.9. Safety Subgroup Analyses

Select safety data may be presented by age, gender, and/or race subgroups. Details will be provided in the SAP.

14.3.6. Pharmacokinetic Analysis

Serum and urine concentrations and PK parameters for lurasidone injectable suspension and its metabolites in serum and urine will be listed and summarized descriptively by dose level, and subdivided by gender in tabular or graphical formats, as appropriate. Descriptive summaries will include number of subjects, mean, standard deviation, coefficient of variation (CV%), minimum, median, maximum, geometric mean, and geometric CV%. C_{max}, t_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ for lurasidone injectable suspension will be the primary PK parameters and all others will be secondary PK parameters.

Dose proportionality of lurasidone injectable suspension will be assessed using a power model for C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ of lurasidone injectable suspension with a formula of ln (PK parameter) = $\alpha + \beta$ ln (dose level).

The estimate of the slope (β), together with its 90% CI will be calculated from the model. Dose proportionality assessment will be performed for the dose range studied.

14.3.7. Pharmacodynamic Analyses

The pharmacodynamic variable is change from baseline in PANSS total score. The pharmacodynamic variable will be analyzed by mixed model for repeated measures (MMRM) method. The MMRM model will include treatment, time, baseline score, and treatment-by-time interaction. Details will be provided in the SAP.

14.3.8. Interim Analysis

There is no planned interim analysis for this study.

14.3.9. Treatment of Missing Data

For analyses of change from baseline, baseline will generally be defined as the predose assessment on Day 1 as scheduled. If this value is unavailable, the last non-missing value prior to dosing will be used. Otherwise, missing observations will be treated as missing at random, and no data imputation will be performed.

Details of incomplete/missing dates for any endpoint will be provided in the SAP.

15. PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL/ DATA COLLECTION, MANAGEMENT, AND QUALITY ASSURANCE

15.1. Data Collection/Electronic Data Capture (EDC)

The results from Screening and data collected during the study (except clinical laboratory test results) will be recorded in the subject's electronic CRF. The study centers will use an EDC system that is compliant with relevant FDA regulatory requirements per 21 CFR Part 11 (Medidata Rave). Password protected access to the EDC system will be via a secure website. Data queries and data corrections will be handled through the same system. All transactions within the EDC system are fully documented within an electronic audit trail. Each set of completed CRFs must be reviewed and electronically signed and dated by the Investigator.

15.2. Computerized Systems Used for Source Data

A list of the computerized systems that will be used to create, modify, maintain, archive, retrieve, or transmit source data are presented below, pursuant to the Guidance for Industry Computerized Systems Used in Clinical Investigations, May 2007.

Table 6: Computerized Systems Used for Source Data

Protocol Step	Computerized System Type or Description
Informed Consent	A
Inclusion/Exclusion Criteria	A
Medical and Psychiatric History	A
Demographics	A
Physical Examination	A
Height	A
Weight and BMI	A
Vital Sign Measurements	A
12-Lead ECG	A
Clinical Laboratory Tests	B
Serum Prolactin	B
Serology	B
Serum Pregnancy Test (females)	B
Urine Drug Screen	B
Urine Cotinine	B
Urine Alcohol Test	B
Blood Sampling for Serum PK	B
Urine Samples for PK assessment	B
Psychotropic Medications	A
Columbia-Suicidality Severity Rating Scale (C-SSRS)	A
Positive and Negative Syndrome Scale (PANSS)	A
Clinical Site Admission	A
Awaken Subject	A
Provide Meals	A
Randomization	A
Oral Lurasidone Administration	A
Lurasidone or Placebo Injection Administration	A
Schedule Next Visit	A
Clinical Site Discharge	A
Concomitant Medications	A
Pretreatment Events	A
Adverse Events	A
Injection Site Reaction Assessment (Investigator)	A
Injection Site Pain (Subject)	A
Statistical analysis	SAS®, version 9.4 or higher

A = EDC; B = LIMS; C = eCOA.

Abbreviations: EDC = electronic data capture; eCOA = electronic clinical outcome assessments; LIMS = laboratory information management system.

15.3. Study Monitoring

This study will be monitored from initiation to completion by the Sponsor or its representative. Monitoring will include personal visits and telephone communication to assure that the investigation is conducted according to protocol and in order to comply with ICH GCP. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each subject.

15.4. Audits

The study may be subject to audit by the Sponsor/designee. If such an audit occurs, the Investigator must agree to allow access to required subject records. This is dependent on the subject granting consent by signing the ICF. By signing this protocol, the Investigator grants permission to personnel from the Sponsor or its representatives for on-site monitoring and auditing of all appropriate study documentation, as well as on-site review of the procedures employed in CRF generation, where clinically appropriate.

In accordance with ICH GCP the Sponsor may select this study for audit. During the audit the Sponsor representative will carry out an inspection of center facilities (eg, pharmacy, drug storage areas, laboratory) and review study related records in order to evaluate the study compliance with the Sponsor/center SOPs, protocol, ICH GCP and local regulations. The Investigator or appropriate designee must also agree to inspection of all study documents by the regulatory authorities and the IEC. Should the Investigator or appropriate designee be notified of a regulatory inspection involving this study they should notify the Sponsor immediately.

15.5. Study Documentation

Study records are comprised of source documents, CRFs, and all other administrative documents, eg, IRB/IEC correspondence, clinical study materials and supplies shipment manifests, monitoring logs, Sponsor and CRO correspondence, etc. A study specific binder will be created and will follow standard practices the maintenance of study records.

Source document is defined as any hand written or computer generated document that contains medical information or test results that have been collected for or are in support of the protocol specifications, eg, clinical laboratory reports, clinic notes, drug disbursement log, subject sign in sheets, subject completed questionnaires if applicable, telephone logs, ECGs, etc. All draft, preliminary and pre-final iterations of a final report are also considered to be source documents, eg, faxed laboratory reports and hard copy laboratory reports, faxed initial results and hard copy, final report.

15.6. Clinical Laboratory Certification and Normal Values

A local laboratory will be used for analysis for most of the clinical laboratory tests for this study. The local laboratory will provide the Investigator, Sponsor/CRO with laboratory certification(s), lab director’s curricula vitae and a dated copy of normal range values.

16. ETHICAL AND REGULATORY OBLIGATIONS

16.1. Study Conduct

The Investigator agrees that the study will be conducted according to the protocol, ICH Good Clinical Practice (GCP), ICH guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will conduct all aspects of the study in accordance with applicable local law(s) and regulation(s).

The Investigator will assure proper implementation and conduct of the study including those study-related duties delegated to other appropriately qualified individuals. The Investigator will assure that study staff cooperate with monitoring and audits.

The Investigator must sign and return to Sponsor/CRO the "Investigator Approval" page.

The Investigator must provide a copy of current curriculum vitae (including a copy of a current medical license, current Drug Enforcement Agency (DEA) license, where applicable), and financial disclosure information. In countries where medical licensure is not issued, the following documentation is acceptable, as applicable:

- Registration number/stamp with a registration number stated on curriculum vitae.
- Appropriate diploma number stated on curriculum vitae.
- Copy of the diploma.

The Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to Sponsor/CRO.

16.2. Institutional Review Board/Independent Ethics Committee

Documented approval for conducting the study from appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be obtained for all participating study centers prior to initiation of the study, according to ICH GCP, applicable local law(s) and regulation(s). When necessary, an extension, amendment or renewal of the IRB/IEC approval must be obtained and also forwarded to the Sponsor. The IRB/IEC must supply the Sponsor a list of the IRB/IEC membership, and a statement to confirm that the IRB/IEC is organized and operates according to ICH GCP, applicable law(s) and regulation(s).

A copy of written IRB/IEC approval or favorable opinion of the protocol, informed consent form and subject recruitment material (if applicable) must be provided to Sponsor/CRO prior to start of the study. The approval or favorable opinion letter must be signed by the IRB/IEC chairman or designee identify the IRB/IEC name and address, identify the clinical protocol by title and/or protocol number, and include the date that approval or favorable opinion was granted. The letter must also contain a statement that the IRB/IEC complies with the requirements in 21 CFR Part 56 for a study conducted under a US IND or ICH GCP, as applicable.

The Investigator/CRO is responsible for obtaining from the IRB/IEC continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not to exceed one year and (if applicable) as otherwise additionally

specified by the IRB/IEC. The Sponsor must be supplied with written documentation of continued review of the clinical research.

The Investigator must promptly inform their IRB/IEC of all SAEs reported by subjects enrolled in the study or other safety information reported from Sponsor/CRO in accordance with applicable law(s) and regulation(s).

16.3. Informed Consent

The Investigator will prepare the informed consent form and provide the form to Sponsor/CRO for approval prior to submission to the IRB/IEC.

The informed consent form will be approved by the Sponsor/CRO prior to submission to the IRB/IEC. The Sponsor/CRO may provide a template informed consent form to be qualified by each research facility to conform to local requirements. All informed consent forms must contain the minimum elements as mandated by ICH GCP, applicable local law(s) and regulations and will be subject to Sponsor/CRO approval as well as IRB/IEC approval. The Sponsor/CRO may submit informed consent forms to a central IRB/IEC for review and approval or favorable opinion contingent upon prior Investigator permission and review.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, allowed to read the approved informed consent form and be provided ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the prospective subject understands the implications of participating in the study, the prospective subject will be asked to give consent to participate in the study by signing the informed consent form. As part of the consent process, each prospective subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection. It should be clearly explained to each prospective subject that participation in each and every clinical visit and assessment is expected. The subject may be discontinued from study medication, but that does not necessarily negate the expectation that the subject will continue to participate in the study through the final visit/assessment. The Investigator will provide a copy of the signed informed consent form to each subject, and will record the date of the informed consent on the CRF.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or if important new information becomes available that may be relevant to the subject's consent, the informed consent form must be revised, submitted to the IRB/IEC for review and approval or favorable opinion. The revised informed consent form must be used to obtain consent from a subject currently enrolled in the study if he or she is affected by the amendment. The revised informed consent form must be used to obtain consent from any new subjects who are enrolled into the study after the date of the approval or favorable opinion of the protocol amendment.

16.4. Subject Privacy

The Sponsor (or Sponsor representative) or any designees affirm uphold the subjects confidentiality. The subject will be identified by unique code only; full names will be masked prior to transmission to the Sponsor. The confidentiality of the subject's personal data shall be protected in accordance with appropriate laws and regulations.

If any cases are identified where the subject's confidentiality has been breached, this must be rectified immediately. All subject identifiable information should be removed and the Sponsor notified.

16.5. Protocol Amendments and Emergency Deviations

All revisions and/or amendments to this protocol must be approved in writing by the Sponsor and the appropriate IRB/IEC. The Investigator will not make any changes to the conduct of the study or the protocol without first obtaining written approval from the Sponsor and the IRB/IEC, except where necessary to eliminate an apparent immediate hazard to a study subject.

Emergency deviations or modifications may be initiated without Sponsor or IRB/IEC approval or favorable opinion, only in cases where the deviation or modification is necessary to eliminate or avoid an immediate apparent hazard to subjects. Emergency deviations or modifications must be reported to the Sponsor/CRO and the IRB/IEC immediately/within five business days of the occurrence, or in accordance with applicable regulatory requirements.

16.6. Records Retention

The Investigator/the study center must arrange for retention of study records at the study center for at least 15 years (or at least 25 years in the EU) from time of participation in the study or longer in accordance with applicable regulations and Sponsor SOPs. The Investigator/site should take measures to prevent accidental or premature destruction of these documents. Documents cannot be destroyed without written Sponsor authorization. The Sponsor will inform the Investigator/the study center when the destruction of documents is permitted.

16.7. Inspection of Records

In the event of an inspection, the Investigator agrees to allow representatives of the Sponsor and its representative and, the regulatory authorities' access to all study records. The Investigator will promptly notify the Sponsor/CRO of all requests to inspect a Sunovion/DSP-sponsored study by government agencies and will promptly forward a copy of all such inspection reports.

16.8. Financial Disclosure

By signing this protocol, the Investigator agrees to provide to the Sponsor prior to start of study accurate financial information to allow the Sponsor to submit complete and accurate certification and disclosure statements as required by the US FDA regulations (21 CFR Part 54). The Investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by the Sponsor. The Investigator will update this information if there are any relevant changes during the conduct of the study and for one year after completion of the study.

The Investigator also consents to the transmission of this information to the Sponsor for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

16.9. Publication Policy

Any formal presentation or publication of data collected as a direct or indirect result of the study will be considered a joint publication by the Investigators and the appropriate personnel of the Sponsor. For multicenter studies, it is mandatory that the first publication is based on all data obtained from all analyses as stipulated in the protocol. Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

The Sponsor will disclose the study results, in the form of a clinical study report synopsis, to the IEC and the applicable regulatory authorities within one year of the end of the study. The format of this synopsis and that of the clinical study report should comply with ICH E3 guidelines for structure and content of a clinical study report.

Investigators participating in multicenter studies must agree not to present data gathered individually or by a subgroup of centers before the full, initial publication, unless this has been agreed to by all other Investigators and by the Sponsor.

16.10. Compensation

If subjects have any adverse event or injury directly resulting from the study medications or procedures, the Sponsor will appropriately compensate in accordance with applicable regulatory requirements.

17. REFERENCES

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18. INVESTIGATOR APPROVAL

I have read the protocol, D1052024, Version 2.00, "A Randomized, Double Blind, Placebo Controlled, Single Ascending Dose Study with Lurasidone Injectable Suspension to Evaluate Safety, Tolerability, and Pharmacokinetics in Subjects with Schizophrenia", and agree that it contains all necessary details for conducting the study and to conduct the study in strict accordance with the specifications outlined herein.

I agree that no additional procedure(s) will be added during the conduct of the study except through protocol amendment by Sunovion Pharmaceuticals Inc. and/or Sumitomo Dainippon Pharma Co., Ltd. and after documentation of IRB approval.

Investigator Signature: _____

Print Investigator Name: _____

Date: _____

19. APPENDIX I. CARDIAC SAFETY MONITORING (ECG)

1. Requirements for Testing

ECG equipment and supplies will be provided by [IQVIA] and should be used for all in-clinic protocol ECG assessments.

- All 12-lead ECGs will be recorded in the same manner.
- The study center personnel must be adequately trained in performing ECGs on the specific ECG equipment used in this protocol that is provided by the cardiac safety vendor.
- To the extent possible, the same ECG machine and personnel should be used to acquire a subject's ECGs throughout the period of their participation in the study.
- ECGs will be recorded with at least one 10-second single-lead tracing recorded from Lead II.

2. Subject Restrictions and Instructions

- Prior to ECG acquisition, the subject will have rested 10 minutes in the supine position and will remain so until the ECG is obtained.

3. Reporting

- It is the responsibility of the Investigator to perform a safety review of the ECG data for changes from previous assessments and/or emergent cardiac dysfunction, and to determine subjects' eligibility or continuance in the study.
- ECGs will be reviewed, signed and dated by the Investigator listed on the Form FDA 1572 (MD or DO) after each ECG collection. The same Investigator should review all ECG reports for a given subject whenever possible.
- For all ECGs, a report will be provided by the cardiac safety vendor to the study center for review and signature.
- The ECG tracing will be kept with subject's source documentation and/or CRF unless it is specified otherwise. The original ECG and the cardiologist's over-read will be retained at the study center.

4. Data Standardization

ECG data will be transmitted to a centralized cardiac safety vendor and centrally over-read and interpreted using standardized procedures.

20. APPENDIX II. CLINICAL LABORATORY TESTS

HEMATOLOGY: (Differential reported as % and absolute value)

Hemoglobin, Hematocrit, Platelet Count, RBC Count, WBC - Total Count, WBC Differential, (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)

BLOOD CHEMISTRIES: Alanine aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate aminotransferase (AST), Bicarbonate (HCO3), Bilirubin (Total, Direct, Indirect), Blood Urea Nitrogen (BUN), Calcium (Ca), Chloride (Cl), Creatinine, Glucose, Magnesium (Mg), Phosphorus (P), Potassium (K), Protein (Total), Sodium (Na), Uric Acid, Albumin

URINALYSIS: Blood, Glucose, Ketones, Leukocyte esterase, Microscopic examination, Nitrites, pH, Protein

LIPID PANEL: LDL-Cholesterol, HDL-Cholesterol, Triglycerides

THYROID PANEL: Free T3, Free T4, Thyroid stimulating hormone (TSH)

COAGULATION PANEL: PT, aPTT, INR

URINE DRUG SCREENING: Amphetamines, Barbiturates, Benzodiazepines, Cannabinoids, Cocaine, Cotinine, Methamphetamines, Methadone, Methylenedioxymethamphetamine (MDMA), Phencyclidine (PCP), Opiates, Oxycodone

SEROLOGY PANEL: Hepatitis B Ag, Hepatitis C Ab, HIV-1 Ab, HIV-2 Ab

OTHER TESTS: Urine Alcohol Test, Serum Pregnancy (β-hCG) (in female subjects only), Urine Pregnancy Test (female subjects only), Serum Prolactin

Laboratory reports will be initialed and dated on all pages by the Investigator listed on the Form FDA 1572 (MD or DO). Laboratory test results will be reviewed by the Investigator as they become available. The Investigator must determine the clinical significance of all out-of-range lab values (except drug screens). Possibly drug-related or clinically relevant abnormal values of uncertain causality must be repeated. Any abnormal values that persist should be followed at the discretion of the Investigator.

21. APPENDIX III. BLOOD AND URINE SAMPLE COLLECTION AND HANDLING GUIDELINES FOR PHARMACOKINETICS

Please refer to the Laboratory Investigator Manual for all collection and shipping instructions.

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

COLLECTION REQUIREMENTS

Collect 4 mL blood sample into a serum separator tube and allow to clot for 30 to 60 minutes at room temperature before centrifugation. The samples will be centrifuged within 1 hour of collection at approximately 2000 g for 10 minutes at approximately 4°C, preferably. To ensure a more homogenous sample, serum sample should first be transferred to 1 tube and mixed well, then split the sample with approximately equal volume into 2 appropriate cryovials/tubes, and label as PKS-Set 1 and PKS-Set 2. Store serum vials at approximately -20°C freezer within 1 hour until shipping to the bioanalytical lab. The date and time of blood collection must be recorded.

URINE SAMPLES

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

To prevent lurasidone nonspecific binding to collection devices, urine samples may be treated with an additive after each void.

Detailed instructions on urine sample collection and treatment after each void will be provided in a Laboratory Manual.

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

The date and time of sample collection must be recorded.

Transfer each individual void/collection in the labeled timepoint storage collector.

Store samples in a freezer at approximately -20ºC until shipping to the bioanalytical lab.

Very important: Do not fill containers/tubes more than 75% of total volume to allow for volume expansion during freezing. Overfilled containers will burst!

SHIPPING:

- Set 1 and Set 2 samples will be shipped in 2 separate shipments to the appropriate laboratory.
- Freeze samples for at least several hours before shipping to the appropriate laboratory.
- All samples will be shipped with dry ice protection.

22. APPENDIX IV. DRUGS KNOWN TO CONSISTENTLY PROLONG THE QT INTERVAL

Generic Name	Trade Name
Amiodarone	Cordarone, Pacerone
Arsenic trioxide	Trisenox
Bepridil	Vascor
Chlorpromazine	Thorazine
Cisapride	Propulsid
Clarithromycin	Biaxin
Disopyramide	Norpace
Dofetilide	Tikosyn
Dolasetron Mesylate	Anzamet
Domperidone	Motilium
Droperidol	Inapsine
Erythromycin	E.E.S., Erythrocin
Gatifloxacin	Tequin
Halofantrine	Halfan
Haloperidol	Haldol
Ibutilide	Corvert
Levomethadyl	Orlaam
Mefloquine	Larium
Mesoridazine	Serentil
Methadone	Dolophine, Methadose
Moxifloxacin	Avelox
Pentamidine	NebuPent
Pentamidine	Pentam
Pimozide	Orap
Probucol	Lorelco
Procainamide	Procan, Pronestyl
Quinidine	Cardioquin, Quiniglute
Sotalol	Betapace
Sparfloxacin	Zagam
Tacrolimus	Prograf
Thioridazine	Mellaril

23. APPENDIX V. ADDITIONAL RESTRICTED SUBSTANCES

CYP3A4 Inducer	CYP3A4 Inhibitor
Carbamazepine	Amiodarone
Phenobarbital	Cimetidine
Phenytoin	Clarithromycin
Pioglitazone	Diltiazem
Rifabutin	Erythromycin
Rifampin	Fluvoxamine
St John's Wort	Grapefruit and grapefruit juice
	Indinavir
	Itraconazole
	Ketoconazole
	Mibefradil
	Nefazodone
	Nelfinavir
	Ritonavir
	Verapamil
	Troleandomycin

This is not an all-inclusive list of restricted enzyme inducers and inhibitors.

24. APPENDIX VI: BODY MASS INDEX DETERMINATION

Body mass index (BMI) will be calculated by measuring the subject's height and weight (both determined without subject wearing shoes) and using these measurements (in centimeters and kilograms) in the following formulae.

Formula:

$BMI = weight\ (kg) \div [height\ (cm) \div 100]^2$

The entries in the following table list the BMI values for subjects of a given height and weight. Please note this table is not inclusive of all possible height and weight combinations.

Body Mass Index (BMI) in kg/m^2 According to Height and Weight

BMI	Height																						
	Cm	142.2	144.8	147.3	149.9	152.4	154.9	157.5	160.0	162.2	165.1	167.6	170.2	172.7	175.3	177.8	180.3	182.9	185.4	188.0	190.5	193.0	195.6
Weight																							
kg																							
40.9		20	20	19	18	18	17	17	16	15	15	15	14	14	13	13	13	12	12	12	11	11	11
43.2		21	21	20	19	19	18	17	17	16	16	15	15	14	14	13	13	13	13	12	12	12	11
45.4		21	22	21	20	20	19	18	18	17	17	16	16	15	15	14	14	14	13	13	13	12	12
47.6		24	23	22	21	21	20	19	19	18	18	17	16	16	16	15	15	14	14	14	13	13	12
49.9		25	24	23	22	22	21	20	20	19	18	18	17	17	16	16	15	15	15	14	14	13	13
52.3		26	25	24	23	23	22	21	20	20	19	19	18	18	17	17	16	16	15	15	14	14	14
54.4		27	26	25	24	23	23	22	21	21	20	19	19	18	18	17	17	16	16	15	15	15	14
56.8		28	27	26	25	24	24	23	22	22	21	20	20	19	18	18	17	17	17	16	16	15	15
59.0		29	28	27	26	25	25	24	23	22	22	21	20	20	19	19	18	18	17	17	16	16	15
61.4		30	29	28	27	26	26	25	24	23	23	22	21	21	20	19	19	18	18	17	17	16	16
63.5		31	30	29	28	27	27	26	25	24	23	23	22	21	21	20	20	19	19	18	18	17	17
65.9		33	31	30	29	28	27	27	26	25	24	23	23	22	21	21	20	20	19	19	18	18	17
68.0		34	33	31	30	29	28	27	27	26	25	24	24	23	22	22	21	20	20	19	19	18	18
70.5		35	34	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	20	20	19	19	18
72.6		36	35	34	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	21	20	20	19
75.0		37	36	35	33	32	31	30	29	28	28	27	26	25	24	24	23	22	22	21	21	20	20
77.1		38	37	36	34	33	32	31	30	29	28	27	27	26	25	24	24	23	22	22	21	21	20
79.5		39	38	37	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23	23	22	21	21
81.6		40	39	38	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23	23	22	21
84.1		42	40	39	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23	23	22
86.2		43	41	40	38	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23	23
88.6		44	42	41	39	38	37	36	35	34	33	32	31	30	29	28	27	27	26	25	24	24	23
90.7		45	43	42	40	39	38	37	36	34	33	32	31	30	30	29	28	27	26	26	25	24	24
93.2		46	44	43	41	40	39	38	36	35	34	33	32	31	30	29	29	28	27	26	26	25	24
95.3		47	45	44	43	41	40	38	37	36	35	34	33	32	31	30	29	29	28	27	26	26	25
97.7		48	47	45	44	42	41	39	38	37	36	35	34	33	32	31	30	29	28	28	27	26	26
99.8		49	48	46	45	43	42	40	39	38	37	36	35	34	33	32	31	30	29	28	28	27	26
102.3		51	49	47	46	44	43	41	40	39	38	36	35	34	33	32	31	31	30	29	28	27	27
104.3		52	50	48	47	45	44	42	41	40	38	37	36	35	34	33	32	31	30	30	29	28	27
106.8		53	51	49	48	46	44	43	42	40	39	38	37	36	35	34	33	32	31	30	29	29	28
109.8		54	52	50	49	47	45	44	43	41	40	39	38	37	36	35	34	33	32	31	30	29	29
111.4		55	53	51	50	48	46	45	43	42	41	40	38	37	36	35	34	33	32	32	31	30	29