- **Protocol number: 31-10-270**
- **Document title: An Open-Label, Multicenter, Rollover, Long-term Study of Aripiprazole Intramuscular Depot in Patients With Schizophrenia**
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Otsuka Pharmaceutical
Development & Commercialization, Inc.

Investigational Medicinal Product

Aripiprazole (OPC-14597)

STATISTICAL ANALYSIS PLAN

for

Protocol No. **31-10-270**
IND No. **67,380**

An Open-Label, Multicenter, Rollover, Long-term Trial of Aripiprazole Intramuscular Depot in Patients with Schizophrenia

Version Final 1.0
Date: December 12, 2018

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1 Introduction

This statistical analysis plan (SAP) documents the statistical methodology and data analysis algorithms and conventions to be applied for statistical analysis and reporting of efficacy and safety data of trial 31-10-270. The first approved protocol, dated 30 Mar 2010, and its amendments (amendment 1 - 23 Nov 2010, amendment 2 - 08 Apr 2013, amendment 3 - 11 Apr 2013, amendment 4 - 08 Jul 2015) are taken into consideration in developing this SAP.

2 Trial Objectives

2.1 Primary Objective

To continue to provide aripiprazole intramuscular (IM) Depot treatment (400 mg or 300 mg) to subjects with schizophrenia completing the 52-week, open-label safety and tolerability trial 31-08-248 (hereafter referred to as trial 248). Subjects can receive this treatment until aripiprazole IM Depot is commercially available in any dosage [including generic formulation(s)] in the country that the trial is being conducted or until the trial end date of 31 Dec 2018 is reached.

2.2 Secondary Objective

The secondary objective of this trial is to collect long-term safety data on aripiprazole IM Depot in addition to what was collected in trial 248 (52-weeks).

3 Trial Design

This is an open-label, multicenter rollover non-comparative trial. The adult subjects with schizophrenia who completed aripiprazole IM Depot treatment in trial 248 are allowed to enroll this trial. No subject who discontinued or did not complete trial 248 are allowed to enroll in this trial. The trial design is presented in Figure 3-1 and Figure 3-2.

Eligible subjects enter this trial directly after completing the end of treatment visit (week 52) of trial 248. The end of treatment evaluations conducted at the last trial visit for trial 248 serve as the baseline evaluations for this trial. Subjects continue to receive aripiprazole IM Depot every month as a continuation of their previous monthly dose in trial 248. The monthly dose can be modified, either reduced from 400 mg to 300 mg to address tolerability or increased from 300mg to 400mg to address efficacy, at the discretion of the investigator.

Following the baseline visit, subjects receive monthly injections and at the same visit, adverse events (AEs) and concomitant medications are recorded and the Columbia

Suicide Severity Rating Scale (C-SSRS) are completed. Every 3 months, all of the monthly assessments are completed along with a urine pregnancy test for women of childbearing potential (WOCBP). Every 6 months, all of the 3-month assessments are completed along with the Clinical Global Impression - Severity (CGI-S) scale, vital signs, and extrapyramidal symptoms (EPS) assessments (including the Abnormal Involuntary Movement Scale [AIMS], Simpson-Angus Scale [SAS], and Barnes Akathisia Rating Scale [BARS]). At the 12-month visit, all of the 6-month assessments are completed along with clinical laboratory tests and assessments of body weight, height, and waist circumference.

Urine drug screening and blood alcohol testing are obtained at baseline and can be re-obtained at the investigator's discretion at any time during the trial. A Visual Analog Scale (VAS) for subject-reported rating of pain at the most recent injection site and the investigator's assessment for pain, redness, induration, and swelling of the most recent injection site are performed at baseline and may be reassessed at the discretion of the investigator. Clinical laboratory tests, physical examination, and electrocardiogram (ECG) obtained at baseline may also be performed at the discretion of the investigator based on clinical necessity.

A Trial Completion visit or Early Termination visit (−2/+10 days) includes the following assessments: C-SSRS, AEs, concomitant medications, a urine pregnancy test for WOCBP, CGI-S, vital signs, EPS assessments (AIMS, BARS, SAS), clinical laboratory tests, and body height and weight.

A 30-Day Post Treatment Follow-up phone call is made 30 days (± 3 days) after it has been determined that the subject no longer participates in this trial and includes questions about any AEs that have occurred and any concomitant medications taken since the last visit

The subject population is comprised of subjects who have completed Trial 248 and in the investigator's judgment may benefit from continued participation in an aripiprazole IM Depot trial, in countries where aripiprazole IM Depot is not commercially available. It is anticipated that 500 to 800 subjects from estimated 250 sites in trial 248 enroll in this trial.

Study Entry	Open Label IM Depot Treatment	Follow up
→	→	→
Study 248 Completers only	Every Month: Injection visits, C-SSRS, AEs, & concomitant medications Every 3 months: CGI-S, vital signs, urine pregnancy test, optional drug and alcohol testing Every 6 months: Injection site assessments Every 12 months: Clinical laboratory tests, PE, ECG, body height & weight, BMI, and waist circumference	One 6-month post End of Study
Week 52 Visit of Study 248 = Baseline for Study 270	*Injection visit window => 28 (-2/+10) days* *Assessment visit windows => -2/+10 days*	*-2/+10 days*

Note: The 3-month, 6-month, and 12-month visits include assessments from the previous visit. For example, the 3-month visit includes all of the monthly visit assessments in addition to the 3-month visit assessments.

Figure 3-1 Trial 31-10-270 Trial Design Schema Prior to Amendment 4

Trial Entry	Open-label IM Depot Treatment	Follow-up
→	→	→
Trial 248 Completers only	Every month: Injection, C-SSRS, AEs, and concomitant medications Every 3 months[a]: Urine pregnancy test for WOCBP Every 6 months[a]: CGI-S, vital signs, and EPS assessments (AIMS, BARS, SAS) Every 12 months[a]: Clinical laboratory tests, body weight and height, and waist circumference	One 30-day post End of Study phone call - AEs and concomitant medications
Week 52 Visit of Trial 248 = Baseline for Trial 270	Injection visit window = 28 (−2/+10) days Assessment visit window = −2/+10 days	± 3 days

[a]The 3-month, 6-month, and 12-month visits include assessments from the previous visit. For example, the 3-month visit includes all of the monthly visit assessments in addition to the 3-month visit assessments. A Trial Completion or Early Termination visit will also be performed.

Figure 3-2 Trial 31-10-270 Trial Design Schema in Amendment 4

4 Sample Size and Power Justification

In this open-label, single arm rollover trial, no formal sample computations were employed. The anticipated number of subjects from Trial 248 that is predicted to enroll in this trial is approximately 500 to 800.

5 Statistical Method

5.1 Data/Data Sets Specifications

5.1.1 Data Sets Analyzed

The following analysis samples are defined for this trial:

- Enrolled Sample: All subjects who sign the informed consents form for the trial and enter the trial.
- Safety Sample: All subjects who receive at least one dose of open-label aripiprazole IM depot.
- Efficacy Sample: All subjects who enter and have at least one post-baseline efficacy evaluation.

Due to the open-label single-arm nature of the trial, all endpoints will be summarized using descriptive statistics. Continuing variables will be tabulated for frequency, mean, median, standard deviation (SD), maximum and minimum. Categorical variables will be tabulated for frequency and percentage. No formal statistical analyses are planned due to the open-label nature of this trial. Subjects who enrolled in this trial rolled over directly from Trial 248. Subjects who enrolled in Trial 248 either rolled over from Trial 31-07-246 or Trial 31-07-247, or directly entered Trial 31-08-248 as *de novo* subjects (i.e., subjects never enrolled in Trial 31-07-246 or 31-07-247). The data will be summarized by enrollment source into Trial 248 as well for all subjects.

5.1.2 Definition of Baseline and Last Visit

Baseline is defined as the last visit with available data in Trial 248. The last visit is defined as the last visit with available data at the completion or on/before early termination. These definitions apply to all efficacy analysis and safety analysis.

5.1.3 Handling Missing Data

Due to nature of this trial design, no missing data are imputed. However, trial days are derived using the formula: Trial Day = Date of assessment - Date of first aripiprazole IM depot injection in trial 270 + 1. Based on the number of trial days, assessments will be mapped into the corresponding trial months in the summary tables as described in Table 5.1.3-1.

Table 5.1.3-1 Mapping of Windows for Trial Months	
Trial Month	**Range of Trial Day**
Month 1	16~44
Month 2	45~74
Month 3	75~105
Month 4	106~135
Month 5	136-165
Month 6	166-196
Month 7	197-226
Month 8	227-256
Month 9	257-287
Month 10	288-317
Month 11	318-347
Month 12	348-379
Month 13	380-409
Month 14	408-439
Month 15	440-470
Month 16	471-500
Month 17	501-530
Month 18	531-561
Month 19	562-591
Month 20	592-621
Month 21	622-652
Month 22	653-682
Month 23	683-712
Month 24	713-744
Month 25	745-774
Month 26	775-804
Month 27	805-835
Month 28	836-865
Month 29	866-895
Month 30	896-926
Month 41	927-956
Month 42	957-987
Month 43	988-1017
Month 44	1018-1047
Month 45	1048-1078
Month 46	1079-1108
Month 47	1109-1138
Month 48	1139-1170
Month 49	1171-1200
Month 50	1201-1230
Month 51	1231-1261
Month 52	1262-1291

Table 5.1.3-1 Mapping of Windows for Trial Months	
Trial Month	**Range of Trial Day**
Month 53	1292-1321
Month 54	1322-1352
Month 55	1353-1382
Month 56	1383-1412
Month 57	1413-1443
Month 58	1444-1473
Month 59	1474-1503
Month 60	1504~~

5.2 Disposition of Subjects

Disposition of subjects for the enrolled sample will be summarized by region, country and center. Subject duration by month and reason for discontinuation will be tabulated for the enrolled sample. Subjects who are evaluated at last scheduled visit during the treatment period are defined as completers. Subjects who are evaluated at the last scheduled visit during the treatment period are defined as completers, i.e., subjects who have their last scheduled visit, or who discontinue due to the commercial availability of trial drug in the country are defined as completers.

5.3 Demographic and Baseline Characteristics

Baseline and demographic characteristics will be summarized using descriptive statistics for the enrolled sample. These characteristics including age, race, ethnicity, gender, weight, height and body mass index (BMI), will be tabulated for the enrolled sample.

5.4 Efficacy Analysis

Change from baseline in CGI Severity (CGI-S) score will be summarized by scheduled visit using descriptive statistics for the efficacy sample. CGI-S score (range 1-7) are directly derived from CGI-S panel.

5.5 Safety Analyses

5.5.1 Adverse Events

All adverse events (AEs) are coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term (Version 21.0 or later). A treatment-emergent AE (TEAE) is defined as an AE which starts after start of trial medication (Aripiprazole IM Depot), or an AE continues from baseline and becomes serious, worsening, trial drug-related or results in death, discontinuation, interruption or reduction of trial medication during this trial. All ongoing AEs and clinically significant AEs from

Trial 248 are recorded as Medical History for this trial. If the AE increases severity or frequency during this trial period, a new AE are recorded. The incidences of the following treatment-emergent adverse events (TEAEs) will be summarized for the safety sample:

- TEAEs by severity
- Potentially drug-related TEAEs
- TEAEs with an outcome of death
- Serious TEAEs
- Discontinuations due to TEAEs

Listing and incidences of AEs described above are tabulated for the safety sample. Deaths, SAEs, and AEs leading to discontinuation from trial or trial treatment are listed for the enrolled sample. In addition, incidences of TEAEs will be provided for the following subgroup analyses: region (US, non-US), sex (male, female), race (Caucasian, Black or African American, American Indian or Alaska Native, Asian, other), age (< 45 years old, ≥ 45 years old), ethnicity (Hispanic or Latino, not Hispanic or Latino), and BMI at baseline (≤ 28 kg/m^2, > 28 kg/m^2).

5.5.2 Clinical Laboratory Tests

Clinical laboratory tests include serum chemistry analysis, hematology analysis, urinalyses and other lab analysis. The potentially clinically relevant laboratory test abnormalities will be listed by subject and by test for the safety sample, respectively. Criteria for the potentially clinically relevant laboratory test abnormalities per protocol are provided in Appendix 1. Per Hy's law, the subjects with AST or ALT ≥ 3 x upper limit of normal value and total bilirubin ≥ 2 x upper limit of normal values will be listed as the potential Hy's law cases. The incidences of potentially clinically relevant laboratory tests abnormalities based on the observation from the scheduled and the unscheduled post-baseline visits will be tabulated. In addition, incidence of potentially clinically relevant laboratory tests in potassium (<= 3.0 mEq/L or >= 5.5 mEq/L) and neutrophils (<= 1500/mm^3) per FDA recommendation will be provided. Summary statistics (frequency, mean, standard deviation, minimum, and maximum) for the clinical laboratory measurements at all scheduled visits, and changes from baseline at scheduled visit and last visits will be presented for the safety sample.

If laboratory tests assessments are repeated for the same visit, the last repeated values are used for summary tables. This is accomplished by sorting patient data by visit date and visit time (if applicable) within the same visit identification. If the lab data are recorded as ranges (i.e., including below or above limit of quantification), these data are not

included in the calculations for changes from baseline but included in the calculations for incidence.

The incidence of prolactin level above the upper limit of normal range (potentially clinically relevant change) will be tabulated by gender and the designated visits for the safety sample. The change from baseline in prolactin levels will be presented by gender at scheduled visit and last visit for the safety sample.

Additionally, incidence of treatment-emergent clinically relevant changes in fasting lipid parameters and glucose (as defined in Table 5.5.2-1) will be summarized for the safety sample.

Table 5.5.2-1 Treatment-emergent Clinically Relevant Changes in Lipids Parameters and Glucose

Parameters	Baseline	Post-baseline
Total Cholesterol(mg/dL), fasting[1]		
	Normal <200	High >=240
	Borderline 200~<240	High >=240
	Normal/Borderline <240	High >=240
	Normal <200	Borderline/High >=200
	Any Value	Increased >=40
LDL Cholesterol(mg/dL), fasting [1]		
	Normal <100	High >=160
	Borderline 100~<160	High >=160
	Normal/Borderline <160	High >=160
	Normal <100	Borderline/High >=100
	Any Value	Increased >=30
HDL Cholesterol(mg/dL), fasting[1]		
	Normal >=40	Low<40
	Any Value	Decreased >=20
Triglycerides(mg/dL), fasting[1]		
	Normal <150	High >=200
	Normal <150	Very High >=500
	Borderline 150~<200	High >=200
	Borderline 150~<200	Very High >=500
	Normal/Borderline <200	High >=200
	Normal/Borderline <200	Very High >=500
	Normal <150	Borderline/High/Very High >=150
	Normal/Borderline /High >=200	Very High >=500
	Any Value	Increased >=40
Glucose(mg/dL), fasting[2]		
	Normal <100	High >=126

Table 5.5.2-1 Treatment-emergent Clinically Relevant Changes in Lipids Parameters and Glucose		
Parameters	**Baseline**	**Post-baseline**
	Impaired Fasting Glucose 100~<126	High >=126
	Normal/ Impaired Fasting Glucose <126	High >=126
	Any Value	Increased >=10

Note: The National Cholesterol Education Program (NCEP) Adult Treatment Program Classifications of lipids (refer to fasting lipid measurements) are used for lipid parameters and the American Diabetes Association Criteria are used for glucose.

5.5.3 Vital Signs Data

Vital signs include body temperature, respiration rate, pulse, systolic blood pressure, and diastolic blood pressure in supine and standing position. In addition, body weight and waist circumference are measured. The potential clinically relevant vital sign abnormalities will be listed by subject. Criteria for the potentially clinically relevant vital sign abnormalities are provided in Appendix 2. Incidences of clinical relevant vital signs abnormalities based on the observation from the scheduled and unscheduled post-baseline visits will be tabulated for the safety sample. In addition to waist circumference and weight, vitals sign parameters at each visit, and change from baseline at the post-baseline visits will be summarized for the safety sample. Body weight changes will be evaluated for the safety sample by calculating mean change from baseline and by tabulating the incidence of >=7% weight gain or loss by visit.

If vital sign assessments are repeated for the same visit, the last repeat values are used for production of summary tables. This is accomplished by sorting patient data by visit date and visit time (if applicable) within the same visit identification.

5.5.4 Electrocardiograms (ECG) Data

All ECG analyses are made using observed data. Baseline is defined as average of ECG measurements at baseline visit as specified in Section 5.1.2. Last visit is defined as defined as average of ECG measurements at last visit as specified in Section 5.1.2. Missing ECG data are not imputed. For the calculation of QT correction by heart rate, QT_c is missing only if all 3 consecutive beats are unreadable. As long as there is at least 1 beat available in the lead, the data are included in the analysis. For each ECG, QT and RR intervals from three consecutive complexes (representing three consecutive heart beats) are measured manually. The QT correction is performed on beat-to-beat basis. The mean of ratios (beat-to-beat) is calculated by (QTc1 + QTc2 + QTc3)/3 using each

QT-RR pair: (QT1, RR1), (QT2, RR2) and (QT3, RR3). The corrected QT intervals for QTcB, QTcF, and QTcN are defined as follows:

- QTcB is the length of the QT interval corrected for heart rate by Bazett's formula: $QTcB = QT / (RR)^{1/2}$.
- QTcF is the length of the QT interval corrected for heart rate by Fredericia's formula: $QTcF = QT / (RR)^{1/3}$.
- QTcN is the length of the QT interval corrected for heart rate by the FDA Neuropharm Division formula: $QTcN = QT/(RR)^{0.37}$.

Potentially clinically relevant ECG abnormalities will be listed by subject. Criteria for potentially clinically relevant ECG abnormalities are provided in Appendix 3. The incidences of abnormal ECGs of potentially clinical relevance based on the observation at the scheduled and the unscheduled post-baseline visits will be tabulated for the safety sample. Descriptive statistics of change from baseline in heart rate and ECG intervals of PR, QRS, RR, QT, QT_cB, QT_cF, and QT_cN will be presented for each scheduled visit and last visit for the safety sample, respectively.

In summarizing the incidence of abnormalities, a subject must have had an evaluation that meets abnormality criteria by the end of trial. Incidence rate will be calculated as the number of subjects having at least one abnormality within the trial divided by the number of subjects who are both exposed to trial medication and have an on-treatment evaluation. In addition, incidences of categorical change in ECG - QTc will be provided for change from baseline >30 millisecond, change from baseline >60 millisecond, new onset >450 millisecond, new onset >480 millisecond and new onset >500 millisecond for the safety sample. Change from baseline in ECG parameters will be calculated at scheduled visit and last visit for the safety sample.

If ECG assessments are repeated for the same visit, the last repeat values are used for production of mean change from baseline. This is accomplished by sorting subject data by visit date and visit time (if applicable) within the same visit identification.

5.5.5 Physical Examination

Physical examination findings will be listed by subject.

5.5.6 Other Safety Data Analysis

5.5.6.1 Special Interested Adverse Events

Incidence of treatment emergent adverse events of special interest, including EPS-related AEs, weight-related AEs, glucose-related AEs, lipid-related AEs, white blood cell abnormalities, orthostasis, prolactin-related AEs, QT-interval AEs, suicidality-related

AEs, and injection-site-related AEs, will be tabulated for safety sample. In addition, proportion of subjects received anticholinergic medication for treatment-emergent EPS-related events will be assessed for safety sample.

5.5.6.2 Extrapyramidal Symptoms Rating Scales

Extrapyramidal symptoms rating scales included the SAS, AIMS, and the BARS. The SAS total score (range 10 to 50) is the sum of the rating scores for 10 items from the SAS panel in the CRF. The AIMS movement rating score (range 0 to 28) is the sum of the rating scores for facial and oral movements (items 1 to 4), extremity movements (items 5 and 6), and trunk movements (item 7). A missing value of any item for the SAS or the AIMS movement scale could result in a missing SAS total score or AIMS movement rating score. The BARS global score (range 0 to5) is derived from the global clinical assessment of akathisia from the BARS panel in the CRF. Mean changes from baseline on the SAS total score, AIMS movement score, and the BARS global score will be summarized by visit in descriptive statistics.

5.5.6.3 Suicidality

Upon administration of the Columbia-Suicide Severity Rating Scale (C-SSRS) assessments, each subject is evaluated for active suicidal ideation with specific plan and intent. Data collected from the C-SSRS assessments will be summarized by the scheduled visit for the safety sample reporting suicidality; suicidal behavior only, emergence of suicidal behavior; suicidal ideation only, emergence of suicidal ideation, emergence of serious suicidal ideation, and worsening of suicidal ideation.

Suicidality is defined as reporting any suicidal ideation or behavior. Suicidal behavior only is defined as reporting any type of suicidal behaviors (actual attempt, interrupted attempt, aborted attempt and preparatory acts or behavior) throughout assessment period. Emergence of suicidal behavior is defined as having no suicidal behavior at baseline and reporting any type of behavior at post-baseline. Suicidal ideation only is defined as reporting any type of suicidal ideation. Emergence of suicidal ideation is defined as having no suicidal ideation at baseline and reporting any type of ideation during treatment. Emergence of serious suicidal ideation is defined as having no suicidal ideation at baseline and reporting serious suicidal ideation with score of 4 or 5 on suicidal ideation severity rating during the treatment. At suicidal ideation severity rating assessment, each person is giving a score of 0 (no ideation present) to 5 (active ideation with plan and intent). Worsening of suicidal ideation is defined as having more severe in most severe suicidal ideation rating at post baseline than at baseline. Numbers of subjects reporting suicidal behavior will be reported by type of suicidal behavior.

Mean and mean change from baseline in suicidal ideation intensity total score for most sever ideation will be summarized by scheduled visit for the safety sample. The suicidal ideation intensity total score is sum of suicidal ideation severity rating scores for frequency, duration, controllability, deterrents and reasons for ideation. For each item, each subject gets the intensity score from 0 (none) to 5 (worst). Therefore, suicidal ideation intensity total score is range from 0 to 25. If the subject did not endorse any suicidal ideation, a score of 0 is given for the intensity scale.

5.5.6.4 Injection Site Reaction and Pain

Injection site reaction and pain are assessed every 6 months in the visual analogue scale (VAS) score (range 0-100mm) before and after IM depot injection at the scheduled visit. Descriptive statistics for VAS score will be tabulated by visit for the safety sample. Assessment pre 1st IM depot injection is used as baseline. Proportions of subjects rated as absent, mild, moderate and severe level by the investigator for localized pain, redness, swelling, and induration will be tabulated by visit for safety sample. In an addition, descriptive statistics for injection site reaction and pain are provided by order of injection.

5.5.7 Other Data Analysis

5.5.7.1 Concomitant Medication

Proportions of subjects from the enrolled sample taking concomitant medications will be tabulated by drug classification using the WHO drug prior to taking trial medication, in the trial period and in the follow-up period, respectively.

Proportions of subjects taking concomitant medications such as benzodiazepine and anticholinergic will be provided. Concomitant medications for benzodiazepine and anticholinergic will be converted into lorazepam equivalent and benztropine equivalent, respectively, using the appropriate conversion factors. Daily dose of benzodiazepine (lorazepam or equivalent) and anticholinergic (benztropine or equivalent) concomitant medications will be summarized. Daily dose for each subject is calculated in total dosage of the specific concomitant medications divided by the duration of subject in the trial period.

5.5.7.2 Duration of Exposure to Trial Medication

Exposure to aripiprazole IM depot for the enrolled sample will be summarized in percentage of subjects receiving injections, average dose level per injection and average trial day of receiving each injection. In an addition, percentage of subjects will be presented by dosing level per injection.

5.5.7.3 Compliance of Trial Medication

To maintain subjects on a schedule within acceptable time window is critical for subjects to achieving and maintaining stability of psychotic symptoms for the completion of this depot trial. A missed dose of IM depot is defined as a lapse of > 38 days between injections. The minimum interval of 26 days and maximum interval of 38 days between injections is to ensure that therapeutic plasma concentrations of aripiprazole are maintained. Compliance of trial medication (aripiprazole IM Depot) will be summarized for the enrolled sample, in proportion of subjects having 100% compliance, along with the following key features of compliance:

- the intervals between Aripiprazole IM depot injections <26 days;
- missing at least 1 injection;
- missing 2 consecutive injections at any time in the trial;
- missing 3 injections within a 52-week time period.

5.5.7.4 Protocol Deviation

Protocol deviations will be listed, and tabulated by protocol deviation type, country and centers. Protocol deviations are specified in the separate documentation: *Programmable Deviation Specification for Protocol 31-10-270.*

Appendix 1 Clinical Relevance Criteria for Laboratory Test Abnormalities

Laboratory Tests	Criterion Values
Chemistry [a]	
AST(SGOT)	≥ 3x upper limit of normal (ULN)
ALT(SGPT)	≥ 3x ULN
Alkaline Phosphates	≥ 3x ULN
LDH	≥ 3x ULN
BUN	≥ 30 mg/dl
Creatinine	≥ 2.0 mg/dl
Uric Acid Male Female	 ≥ 10.5 mg/dl ≥ 8.5 mg/dl
Bilirubin (Total)	≥ 2.0mg/dl
CPK	≥ 3xULN
Prolactin	>ULN
Hematology [a]	
Hematocrit Male Female	 ≤ 37% and ≥ 3% decrease from baseline ≤ 32% and ≥ 3% decrease from baseline
Hemoglobin Male Female	 ≤ 11.5 g/dl ≤ 9.5 g/dl
White Blood Count	≤ 2,800 /mm^3 or ≥ 16,000 /mm^3
Eosinophils	≥ 10%
Neutrophils	≤ 15%
Platelet Count	≤ 75,000 /mm^3 or ≥ 700,000 /mm^3
Urinalysis [a]	
Protein	Increase of ≥ 2 units
Glucose	Increase of ≥ 2 units
Casts	Increase of ≥ 2 units
Additional Criteria	
Chloride	≤90 mEq/L or ≥ 118 mEq/L
Potassium	≤2.5 mEq/L or ≥ 6.5 mEq/L
Sodium	≤126 mEq/L or ≥ 156 mEq/L
Calcium	≤8.2 mg/dL or ≥ 12 mg/dL
Glucose Fasting Non-Fasting	 ≥ 115 mg/dL ≥ 200 mg/dL
Total cholesterol, Fasting	≥ 240 mg/dL
LDL cholesterol, Fasting	≥ 160mg/dL
HDL cholesterol, Fasting	≤ 30 mg/dL
Triglycerides, Fasting Male Female	 ≥ 160 mg/dL ≥ 120 mg/dL

[a] As defined in "Supplementary Suggestions for Preparing an Integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in Periodic Safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87).

Appendix 2 Clinical Relevance Criteria for Vital Sign Abnormalities

VARIABLE	CRITERION VALUE [a]	CHANGE RELATIVE TO BASELINE [a]
HEART RATE [b]	>120 BPM <50 BPM	INCREASE OF ≥ 15 DECREASE OF ≥ 15
SYSTOLIC BLOOD PRESSURE [b]	>180 MMHG <90 MMHG	INCREASE OF ≥ 20 DECREASE OF ≥ 20
DIASTOLIC BLOOD PRESSURE [b]	>105 MMHG <50 MMHG	INCREASE OF ≥ 15 DECREASE OF ≥ I5
ORTHOSTATIC HYPOTENSION	≥ 20 MMHG DECREASE IN SYSTOLIC BLOOD PRESSURE AND ≥ 25 BPM INCREASE IN HEART RATE FROM SUPINE TO SITTING/STANDING	
WEIGHT	-	INCREASE ≥ 7% DECEASE ≥ 7%
TEMPRATURE	≥37.8°C	INCREASE ≥1.1°C

[a] In order to be identified as "clinically relevantly abnormal," an on-drug value must meet the "Criterion Value" and also represent a change from the patient's pretreatment value of at least the magnitude shown in the "Change Relative to Baseline column.

[b] As defined in "supplementary suggestions for Preparing an integrated Summary of Safety Information in an Original NDA Submission and for Organizing Information in period safety Updates," FDA Division of Neuropharmacological Drug Products draft (2/27/87)

Appendix 3 Clinical Relevance Criteria for ECG Abnormalities

Variable	Criteria/Change relative to Baseline
Rate	
Tachycardia	≥ 120 bpm and increase of ≥ 15 bpm
Bradycardia	≤ 50 bpm and decrease of ≥ 15 bpm
Rhythm	
Sinus tachycardia	≥ 120 bpm and increase of ≥ 15 bpm
Sinus bradycardia	≤ 50 bpm and decrease of ≥ 15 bpm
Supraventricular premature beat	Not present → present
Ventricular premature beat	Not present → present
Supraventricular tachycardia	Not present → present
Ventricular tachycardia	Not present → present
Atrial fibrulation	Not present → present
Atrial flutter	Not present → present
Conduction	
1^0 A-V Block	PR ≥ 0.20 sec and increase of ≥ 0.05 sec
2^0 A-V Block	Not present → present
3^0 A-V Block	Not present → present
Left bundle-branch block	Not present → present
Right bundle-branch block	Not present → present
Pre-excitation syndrome	Not present → present
Other intraventricular conduction block	QRS ≥ 0.12 sec and increase of ≥ 0.02 sec
Infarction	
Acute or Subacute	Not present → present
Old	Not present - present at ≥ 12 weeks post entry into the trial
ST/T Morphology	
Myocardial Ischemia	Not present → present
Symmetrical T-wave inversion	Not present → present
QTc	≥ 450 msec and ≥ 10% increase from baseline

Appendix 4 Table of Contents for Tables and Listings

Clinical Summary Tables

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CT-8.5.3	INCIDENCE OF SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS BY SYSTEM ORGAN CLASS AND MEDDRA PREFERRED TERM AND SEVERITY
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