SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	Not applicable
Name of Active Ingredient(s)	Risperidone

Protocol No RIS-SCH-1012

Title of Study: Single-Dose, Open-Label Pilot Study to Explore the Pharmacokinetics, Safety and Tolerability of a Gluteal Intramuscular Injection of a 4-Week Long-Acting Injectable Formulation of Risperidone in Subjects With Chronic Stable Schizophrenia

Principal Investigator: Dr Riesenberg, MD – Atlanta Center for Medical Research, Georgia 30308-1311, United States

Publication (Reference): None

Study Period: 29 December 2008 to 19 June 2009

Phase of Development: 1

Objectives: The primary objective of this study was to explore the pharmacokinetics (PK) of a 4-Week long acting injectable (LAI) formulation of risperidone after single IM injection of 75 mg in the gluteal muscle.

Secondary objectives were to: evaluate the safety and tolerability of a 4-Week LAI formulation of risperidone after single IM injection of 75 mg in the gluteal muscle; explore the feasibility to define an in vitro-in vivo correlation (IVIVC, optional).

Methods: This was an open-label, multicenter, exploratory study comprising a pretreatment screening phase (≤21 days), an open-label treatment phase (comprising 2 treatment periods), and end-of-study (EOS) evaluations. Subjects were allowed to continue on their existing oral antipsychotic treatment throughout the study. All subjects received a single IM injection of risperidone 1 mg immediate release (IR) in the gluteal muscle in Period 1 and a single IM injection of risperidone 75 mg 4-Week LAI in the gluteal muscle in Period 2.

Number of Subjects (planned and analyzed): Planned: Approximately 26 subjects were planned to be enrolled to ensure that approximately 20 subjects completed all required assessments. Analyzed: Twenty of the 24 enrolled subjects completed the study. Twenty-one out of 24 subjects received both 1 mg IR in the gluteal muscle in Period 1 and a single IM injection of risperidone 75 mg 4-Week LAI in the gluteal muscle in Period 2. Seventeen subjects were included in the comparative statistics for PK parameters for the active antipsychotic fraction (AAF).

Diagnosis and Main Criteria for Inclusion: Men and women between 18 and 55 years of age inclusive, BMI between 18 and 35 kg/m^2, with a diagnosis of chronic schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders - fourth edition, and stable without any changes in antipsychotic medications or dosage during the 4 weeks before the screening visit, were included.

Mode of administration and Duration of Treatment: Risperidone 4-Week LAI formulation was administered as an IM injection of 75mg risperidone. The reference therapy, risperidone IR solution, was administered as an IM injection of 1 mg of risperidone. The total duration of the study for each subject was 14 to 18 weeks.

Criteria for Evaluation:

Pharmacokinetics: Venous blood samples (4 mL each) for determination of risperidone and 9-hydroxy-risperidone plasma concentrations were analyzed using a liquid chromatography coupled to tandem mass spectrometry method. The following PK parameters were estimated from plasma data for risperidone, 9-hydroxy-risperidone, and the AAF including: IR and LAI treatment: maximum plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}), area under the plasma concentration-time curve from time 0 to the time of the last observed quantifiable concentration (C_{last}) (AUC_{last}), first-order rate constant associated with the terminal portion of the curve (λ_z), elimination half-life associated with the terminal slope of the semilogarithmic drug concentration-time curve ($t_{1/2}$), percentage of AUC_∞ obtained by extrapolation ($\%AUC_{\infty,ex}$). For LAI treatment: time between drug administration and start of absorption (t_{lag}), $F_{rel\ LAI/IR}$ for dose-normalized AUCs.

Pharmacodynamics: No pharmacodynamic assessments were performed.

Safety: Safety evaluations included adverse event (AE) monitoring, physical examinations, 12-lead electrocardiograms (ECGs), vital signs measurements, clinical laboratory evaluations (hematology, serum chemistry, and urinalysis), Extrapyramidal Symptom Rating Scale (ESRS), Clinical Global Impression - Severity (CGI-S), injection site evaluation by Visual Analog Scale (VAS) (by subject: VAS-A [pain during injection] and VAS-B [pain at injection site before and after injection at specified timepoints]).

Statistical Methods:

Sample Size Determination: To sufficiently characterize the PK of the risperidone 4-Week LAI formulation, approximately 26 subjects were to be selected to ensure that approximately 20 subjects completed both periods of the study. Based on an estimated intersubject coefficient of variation (CV) of 55% and a sample size of 20, the estimate of the mean PK parameter values would fall within 77% to 130% of the true value, with 95% confidence interval (CI). Based on an estimated intrasubject CV of 36% and a sample size of 20, the estimate of the ratio of mean PK parameter values (LAI/IR) would fall within 82% to 122% of the true value, with 90% CI.

Pharmacokinetics: For each treatment, descriptive statistics were calculated for the plasma concentrations (risperidone, 9-hydroxy-risperidone, AAF) at each sampling time and for all PK parameters, per treatment. The parameters of interest to evaluate the relative bioavailability of risperidone 4-Week LAI versus risperidone 1 mg IR after gluteal injection were the log-transformed estimated AUCs (AUC_{last}, AUC_∞) from Period 1 and Period 2. A mixed-effects analysis of variance model that included treatment (risperidone IR, risperidone 4-Week LAI) as fixed effect, and subject as a random effect was used to estimate the least squares means (LSM) and intrasubject variance. Using these estimated LSM and intrasubject variance, the point estimate and 90% CI for the difference in means on a log scale between risperidone 4-Week LAI and risperidone IR was constructed. The limits of the CI were retransformed using antilogarithms to obtain 90% CI for the ratios of the mean AUCs of risperidone 4-Week LAI versus risperidone IR.

Safety: Safety data were evaluated using incidence of treatment-emergent AEs (TEAEs) for each treatment. Descriptive statistics for demographics and baseline characteristics were calculated. Changes from baseline in ESRS scores, CGI-S scores, clinical laboratory results, vital signs, and ECG parameters were summarized by treatment and/or timepoint.

RESULTS:

Twenty of the 24 randomized subjects completed the study. Four subjects were discontinued from the study: 1 due to AE (dilated cardiomyopathy, considered by the investigator to be doubtfully related to the study drug; the subject died on Day 4 in Period 1, prior to administration of the 4 Week LAI formulation); 2 due to withdrawal of consent (1 in Period 1 and 1 in Period 2) and 1 for other reasons (subject was withdrawn in Period 1 upon sponsor's request).

All the subjects (8 women and 16 men) were diagnosed with paranoid schizophrenia (but otherwise healthy), between 20 to 55 years of age (inclusive), with a BMI ranging from 19 to 35 kg/m^2.

PHARMACOKINETIC RESULTS: The release profile of the risperidone 4 Week LAI formulation demonstrated some variability, with some subjects showing a slow release, and a subset demonstrating

a more significant early release. In general, therapeutic drug concentrations were reached 2 weeks after injection, remained fairly constant for an additional 2 to 3 weeks, and decreased monoexponentially afterwards. The relative bioavailability after IM gluteal injection with the risperidone 4 Week LAI compared with the risperidone IR formulation was 103% (geometric mean ratio).

SAFETY RESULTS: The risperidone 4-Week LAI formulation at the dose of 75 mg was generally well tolerated in the 21 stable schizophrenia subjects who received the injection.

Nineteen (79%) of 24 subjects experienced at least 1 TEAE in this study. Overall, the most commonly reported TEAEs were fatigue (25%), somnolence (17%), and weight increased (17%). Most TEAEs were mild in severity.

In Period 2 (4-Week LAI single injection), no serious AEs (SAEs) were reported with a causal relationship to the study drug. The most commonly (>10%) reported AEs in Period 2 were: somnolence (3 subjects, 14%), fatigue (3 subjects, 14%) and increased weight (3 subjects, 14%).

In Period 1 (IR formulation), the most commonly (>10%) reported AE was fatigue (5 subjects, 21%).

Three subjects experienced 1 or more SAEs in this study. Two SAEs were reported for 1 subject: hepatic enzyme increase and cardiomyopathy, resulting in death. Both SAEs were considered to be doubtfully related to the study drug; cause of death was determined to be dilated cardiomyopathy. No concomitant medication was prescribed for these AEs. Two other subjects in Period 2 reported SAEs of anxiety and inadequate housing, considered to be unrelated to the study drug.

There were no cases of post injection severe sedation associated with the risperidone 4-Week LAI formulation. Injection site reactions in Period 2, as evaluated by both investigators and subjects, were mild in nature and similar to results obtained from previous trials for the 2-week LAI formulation.

Three subjects reported treatment-emergent dystonia (75 mg LAI), restless leg syndrome (75 mg LAI), and parkinsonism (1 mg IR) during the study. The events of restless leg syndrome and parkinsonism were reported to persist at the EOS visit. One subject had moderate galactorrhoea and mild postural orthostatic tachycardia syndrome in Period 2 (75 mg LAI), which resolved at the EOS.

No glucose-related AEs were reported during the study, and there were no clinically noteworthy mean changes observed in clinical laboratory parameters, vital signs, and ECG parameters throughout the study. No suicide related AEs were reported.

STUDY LIMITATIONS: To ensure subjects had adequate treatment coverage, antipsychotics other than risperidone, and other concomitant medications used to manage the subjects' schizophrenia were allowed during the study. Therefore, safety results should be interpreted in light of these concomitant medications.

CONCLUSION: The release profile of the risperidone 4-Week LAI formulation showed a variable release profile.

Therapeutic drug concentrations were reached 2 weeks after injection, remained fairly constant for an additional 2 to 3 weeks, and decreased mono-exponentially afterwards. The relative bioavailability after IM gluteal injection with the risperidone 4-Week LAI, compared with the risperidone IR formulation was 103%.

The risperidone 4-Week LAI formulation at the dose of 75 mg was generally well tolerated in the 21 stable schizophrenia subjects dosed.

Injection site reactions observed were comparable with the 2-Week formulation.

Adverse events observed were comparable with previous studies, and consistent with the safety profile of the compound.

No specific safety issues were observed related to the formulation.

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