CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development	
Name of Finished Product	RISPERDAL® CONSTA®	
Name of Active Ingredient(s)	Risperidone	

Protocol No.: RISSCH1007 (CR011023)

Title of Study: Comparative single-dose pharmacokinetics and safety of gluteal and deltoid intramuscular injection of long-acting injectable risperidone in subjects with chronic stable schizophrenia.

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Publication (Reference): None

Study Period: 13 October 2005 - 27 March 2007	**Phase of Development:** 1

Objectives: The primary objective of the study was to determine whether the 37.5-mg and 50-mg doses of LAI risperidone injected in the deltoid muscle resulted in a systemic exposure higher than that obtained with 25 mg LAI risperidone injected in the gluteal muscle but not exceeding that obtained with 50 mg LAI risperidone injected in the gluteal muscle.

Secondary objectives were to: characterize the rate and extent of absorption after i.m. injection of LAI risperidone in the deltoid muscle relative to the gluteal muscle and perform associated bioequivalence statistics; document the local injection site tolerability; assess safety and tolerability.

Methodology: This was a randomized, open-label, single dose, multicenter, 2-way crossover study comprising a screening phase, two open-label treatment periods, and end-of-study evaluations. Subjects were allowed to continue on their existing oral antipsychotic treatment throughout the study, if not receiving disallowed medications, per protocol.

Subjects were randomised to 1 of 2 parallel panels. In each panel, subjects received a single intramuscular (i.m.) injection of LAI risperidone in each treatment period in a 2-way crossover design. In Panel I, subjects received 25 mg LAI risperidone via the gluteal muscle and 37.5 mg LAI risperidone via the deltoid muscle during the study period. In Panel II, subjects received 50 mg LAI risperidone via the gluteal muscle and 50 mg LAI risperidone via the deltoid muscle during the study period. All injections were given in 2 mL diluent, with a 1-inch needle for deltoid injection and a 2-inch needle for gluteal injection.

There were 2 global amendments to the original protocol: Amendment INT-1 (September 2005) clarified the procedure for the subject's evaluation of injection site pain, and corrected an error regarding the gauge of the needle required for deltoid injection; Amendment INT-2 (November 2006) was introduced to code adverse events using the Medical Dictionary for Regulatory Activities (MedDRA) rather than World Health Organization Adverse Reaction Terminology (WHOART).

Number of Subjects (planned and analyzed): It was planned to enroll approximately 150 subjects to ensure that 130 subjects (54 subjects in Panel I and 76 subjects in Panel II) completed all study evaluations.

Across GCP compliant sites, 170 subjects were enrolled (64 in Panel I and 106 in Panel II) and 135 subjects completed all study procedures (51 in Panel I and 84 in Panel II). An additional 18 subjects were enrolled at a site with potential GCP noncompliance issues (Site #048001). These subjects were not included in the pharmacokinetic analysis and summaries of safety. The safety data on these patients are described separately.

Data from all 170 subjects at GCP compliant sites were included in the pharmacokinetic analysis. The primary pharmacokinetic parameters (C_{max} and AUC) were available in at least one study period for 157 subjects (57 subjects in Panel I, 100 subjects in Panel II) and 137 subjects had PK parameters available in both study periods (52 subjects in Panel I, 85 subjects in Panel II).

Diagnosis and Main Criteria for Inclusion: Male or female subjects, aged between 18 and 55 years inclusive, with a diagnosis of stable, chronic schizophrenia of any subtype, according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Subjects were to have a body mass index (BMI) between 18.0 and 35.0 kg/m^2, inclusive, and were to be otherwise healthy on the basis of a screening physical and medical examination.

SYNOPSIS (CONTINUED)

Test Product, Dose and Mode of Administration, Batch No.: LAI risperidone (25 mg, 37.5 mg or 50 mg) was administered by i.m. injection (gluteal and deltoid muscle) in 2 mL of diluent using a safety needle (1 inch, 21 gauge for deltoid injection; 2 inches, 20 gauge for gluteal injection). Batch numbers and expiry dates for the study drug products are provided below:

Dosage/Product	Batch Number	Expiry Date
Diluent	508014	25-February-2009
25 mg LAI risperidone	164-0943BB	04-April-2007
37.5 mg LAI risperidone	164-2393CA	27-August-2007
50 mg LAI risperidone	164-2194AB	06-August-2008

LAI = long-acting injectable

Reference Therapy, Dose and Mode of Administration, Batch No.: None.

Duration of Treatment: Single i.m. injection in each of the 2 treatment periods. In each treatment period, study drug administration was followed by an 85-day observation period during which subjects continued their ongoing oral antipsychotic treatment as permitted by the protocol.

Criteria for Evaluation:

Pharmacokinetics: Blood samples for pharmacokinetic analyses were collected predose and at predefined time points up to 85 days after dosing. Risperidone and 9-hydroxy-risperidone plasma concentrations were determined using a validated LC-MS/MS method. The concentrations of the active moiety were calculated as the sum of risperidone and 9-hydroxy-risperidone.

Based on the plasma concentration-time data of individual subjects and using the actual sampling times, the following pharmacokinetic parameters of risperidone, 9-hydroxy-risperidone, and the active moiety were estimated: C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $\%AUC_{\infty,ex}$, λ_z, and $t_{1/2}$.

Pharmacodynamics: No pharmacodynamic assessments were performed.

Safety: Adverse events, Extrapyramidal Symptom Rating Scale (ESRS), physical examination, 12-lead ECG, vital signs, clinical laboratory tests (hematology, serum chemistry, and urinalysis).

Local Tolerability: The investigator and the subject evaluated the injection site 30 minutes before injection and at 2, 12 and 24 hours after each i.m. study drug injection, and on Days 3 and 15.

Pharmacogenomics: Whole blood was taken for (optional) genetic analysis from subjects who gave informed consent for this part of the study.

Statistical Methods:

Pharmacokinetics: For each treatment, descriptive statistics were calculated for plasma concentrations at each time point, and for all pharmacokinetic parameters of the active moiety, risperidone and 9-hydroxy-risperidone.

A mixed effect ANOVA model was run on the primary parameters of interest: the AUCs (AUC_{last} and AUC_{∞}) and C_{max}. The treatment comparisons of interest were Treatment B (37.5-mg deltoid) versus A (25-mg gluteal), and Treatment D (50-mg deltoid) versus C (50-mg gluteal). The analysis was performed on log-transformed estimated PK parameters. Treatment B was to be considered superior, in terms of plasma exposure, to Treatment A if the lower bound of the 90% confidence intervals for the ratio of the means (B/A) was higher than 100%. Treatment D was to be considered not superior in plasma exposure to Treatment C if the higher bound of the 90% confidence interval for the ratio of the means (D/C) was lower than 125%. Deltoid and gluteal injections were to be considered bioequivalent administration routes if for C_{max} and AUC the 90% confidence intervals for the ratio of means D/C (50 mg) fell within the 80% to 125% acceptance bounds. In addition to the planned analyses, an ANOVA was performed to compare Treatment B (37.5-mg deltoid) to Treatment A (25 mg-gluteal) after dose-normalization to 25 mg.

In further characterizing the pharmacokinetics of LAI risperidone, dose-proportionality was explored by cross-panel graphical comparison, and by statistical analysis (ANOVA) for the deltoid muscle (50 mg versus 37.5 mg) and the gluteal muscle (50 mg versus 25 mg) separately, all based on dose-normalized PK parameters (C_{max}, AUC_{last}, and AUC_{∞}) for the active moiety, risperidone and 9-hydroxy-risperidone.

Safety and Local Tolerability: Safety and local tolerability data were listed and summarized for each treatment. No formal statistical analysis was performed.

SYNOPSIS (CONTINUED)

SUMMARY - CONCLUSIONS

One hundred seventy subjects with schizophrenia were enrolled in the study and 135 subjects completed the study. Thirty-five subjects (21%) discontinued from the study. Two subjects were withdrawn due to an adverse event. One subject died before completing the study and another subject died after withdrawing consent. No subjects discontinued from the study for reasons that were considered related to the injection site.

An additional 18 subjects were recruited and received at least one dose of study drug at a potentially GCP noncompliant site (Site #048001). These subjects were excluded from the safety and pharmacokinetic analyses, as the integrity of the data could not be confirmed.

PHARMACOKINETICS:

Mean (± SD) Pharmacokinetic Parameters of Active Moiety (PK Analysis Set)

	25 mg LAI gluteal		37.5 mg LAI deltoid		50 mg LAI gluteal		50 mg LAI deltoid	
Parameter	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
				Active Moiety				
t_{max} (days)	55	30.56 ± 6.90	54	30.71 ± 6.34	94	28.99 ± 6.34	91	30.57 ± 5.90
C_{max} (ng/mL)	55	22.8 ± 13.7	54	35.4 ± 32.4	94	41.1 ± 18.9	91	37.8 ± 17.2
AUC_{last} (ng.h/mL)	55	7433 ± 9908	54	12462 ± 22692	94	11016 ± 4838	91	10369 ± 3851
$t_{½}$ (days)	49	6.1 ± 5.8	48	8.3 ± 8.2	82	6.1 ± 6.8	81	8.1 ± 10.9
AUC_{∞} (ng.h/mL)	52	5721 ± 2209	52	8334 ± 3322	91	10794 ± 4443	90	10370 ± 3827

Injection of a single 37.5-mg dose of LAI risperidone in the deltoid muscle resulted in a systemic exposure that was higher than the exposure obtained after injection of a single 25-mg dose in the gluteal muscle. After dose normalization, a single 37.5-mg dose of LAI risperidone injected in the deltoid muscle was bioequivalent to 25 mg LAI risperidone injected in the gluteal muscle, with respect to peak and total exposure. The limits of the 90% confidence intervals for the ratios of dose-normalized C_{max} and AUC values of the active moiety, risperidone and 9-hydroxy-risperidone fell entirely within the 80-125% equivalence range.

Intramuscular injection of 50 mg LAI risperidone in the deltoid muscle was bioequivalent, with respect to peak and total exposure, to 50 mg LAI risperidone injected into the gluteal muscle. The limits of the 90% confidence intervals for the ratios of C_{max} and AUC values of the active moiety, risperidone and 9-hydroxy-risperidone fell entirely within the 80-125% equivalence range.

Summary of Within-Panel Statistical Comparison of PK Parameters of Active Moiety

(PK Statistical Analysis Set)

Substance	PK Parameter	Number of Subjects (Test/Ref)	Test LSM	Reference LSM	Estimated Ratio (%)	90% CI
Panel I, 37.5 mg deltoid DN[a] (test) versus 25 mg gluteal (reference)						
Active Moiety	$AUC_{¥}$	50/50	5116.15	5224.70	97.92	(89.95 ; 106.60)
	AUC_{last}	52/52	5636.39	5648.87	99.78	(91.43 ; 108.89)
	C_{max}	52/52	19.58	19.93	98.24	(87.54 ; 110.24)
Panel II, 50 mg deltoid (test) versus 50 mg gluteal (reference)						
Active Moiety	$AUC_{¥}$	81/81	9553.96	9987.54	95.66	(90.33 ; 101.30)
	AUC_{last}	85/85	9657.39	10282.79	93.92	(88.47 ; 99.70)
	C_{max}	85/85	33.70	37.73	89.31	(82.86 ; 96.26)

PK parameters were analyzed on logarithmic scale, but statistics back transformed to original scale.

Results are least-square geometric means (LSM)

Ratio: ratio of least-squares geometric means, expressed as percentage (100 x test/reference).

[a]Values dose-normalized to 25 mg prior to analysis

Cross-panel graphical comparison for the deltoid muscle (50 mg versus 37.5 mg) and the gluteal muscle (50 mg versus 25 mg) suggested dose proportional pharmacokinetics for the active moiety, risperidone and 9-hydroxy-risperidone, based on dose-normalized PK parameters (C_{max}, AUC_{last}, and AUC_{∞}).

SYNOPSIS (CONTINUED)

SAFETY AND LOCAL TOLERABILITY RESULTS:

LAI risperidone was safe and well tolerated when administered as a single injection in the deltoid muscle (37.5 mg and 50 mg) and gluteal muscle (25 mg and 50 mg). The incidence of treatment-emergent adverse events was similar across all treatment groups (approximately 50%) and there were very few serious adverse events or withdrawals due to adverse events. The most common treatment-emergent adverse events were headache (15%) and nasopharyngitis (12%), both of which are documented adverse drug reactions with LAI risperidone.

Both dosage strengths of LAI risperidone were similarly well tolerated at the deltoid and gluteal injection sites. The majority of subjects had no local injection site findings, based on investigator- and subject-rated evaluations. For those subjects with local injection site findings, most were mild. Local injection site tolerability was slightly better for the gluteal injection than the deltoid injection, though these differences were small and not clinically significant.

CONCLUSION:

Deltoid and gluteal injections of LAI risperidone are bioequivalent administration routes with respect to peak and total plasma exposure.

Intramuscular injections via the deltoid and gluteal sites are equivalent routes of administration of LAI risperidone with respect to local injection site tolerability.

The safety and tolerability profile of LAI risperidone was comparable when administered as an intramuscular injection in the deltoid (37.5 mg and 50 mg) and gluteal (25 mg and 50 mg) sites.

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