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.: RISSCH1008 CR011533

Title of Study: Local-site tolerability of multiple-dose treatment with deltoid intramuscular injection of RISPERDAL CONSTA in subjects with chronic schizophrenia.

Principal Investigator: Mohammed Abdul Bari, M.D.- Synergy Clinical Research Center, National City, CA 91950, USA

Publication (Reference): Not applicable.

Study Period: Clinical Conduct: 01 March 2006 (date of first informed consent) to 05 September 2006 (date of last end of study visit)	**Phase of Development:** 1

Objectives: The primary objective of the study was to evaluate the discontinuation rate of subjects with a diagnosis of schizophrenia receiving multiple sequential 2-mL injections with long-acting injectable (LAI) risperidone (37.5 or 50 mg) when administered into the deltoid muscle once every 2 weeks.

Secondary objectives were to: document clinician-rated parameters of local site injection reactions of redness, swelling, tenderness, and/or induration; document subject-rated local site injection pain; document the pharmacokinetics (PK) of multiple doses of LAI risperidone injected into the deltoid muscle; assess overall safety.

Methodology: This was an open–label, multiple-dose, multicenter study in subjects diagnosed with chronic schizophrenia, who were previously receiving LAI risperidone 25- or 37.5-mg injections into the gluteal muscle, and clinically required a higher dose. The study consisted of a pretreatment screening phase that was planned to be no more than 14 days; an 8-week, open-label treatment phase during which subjects received 4 sequential 2-mL injections with LAI risperidone (37.5 or 50 mg) administered every 2 weeks into the deltoid muscle in alternate arms (right versus left) for each visit; and a post treatment phase consisting of end-of-study evaluations upon completion of all the study procedures on Day 57 (actually occurred up to Day 64) or at early withdrawal.

Number of Subjects (planned and analyzed): Approximately 60 subjects were to be screened to ensure that 50 subjects completed the second injection with LAI risperidone into the deltoid muscle (1 in each arm). In practice, 53 subjects were enrolled in the trial: 51 subjects (96%) received at least 2 deltoid injections. Forty-four subjects (83% of all subjects) completed the study. Fifty-three subjects were included in the PK and safety analysis sets.

Diagnosis and Main Criteria for Inclusion: Subjects were male or female, between 18 and 55 years of age, inclusive, with a diagnosis, according to the DSM-IV, of chronic schizophrenia of any subtype (295.1, 295.2, 295.3, 295.6, 295.9). Eligible subjects must have received gluteal injections with 25 or 37.5 mg LAI risperidone for at least 2 injections (1 month) before participation in the screening phase, and in clinical need of a dosage increase as assessed by the treating physician. Subjects had to be otherwise healthy, and to have a BMI (weight [kg]/height [m]^2) within the range of 18.0 to 35.0, inclusive. Women had to be postmenopausal, surgically sterile, or abstinent, or, if sexually active, had to be practicing an effective method of birth control before entry into and throughout the study.

Test Product, Dose and Mode of Administration, Batch No.: 37.5 mg LAI risperidone (lot number 164-2194BA; expiry date 08 June 2008) and 50 mg LAI risperidone (lot number 164-2194AB; expiry date 08 June 2008) in diluent (batch number 426035; expiry date June 2007) was administered as a single 2 mL i.m. injection in the deltoid muscle.

Subjects who previously received 25 mg or 37.5 mg LAI risperidone into the gluteal muscle received 37.5 mg or 50 mg LAI risperidone, respectively, into the deltoid muscle. LAI risperidone dose for subjects who initially received i.m. deltoid injection with 37.5 mg LAI risperidone could be increased to 50 mg, and LAI risperidone dose for subjects who initially receive i.m. deltoid injection with 50 mg LAI risperidone could be decreased to 37.5 mg. Dose adjustment was not based on local site reactions. Increase of the LAI risperidone dose above 50 mg, or a decrease below 37.5 mg was not allowed.

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

SYNOPSIS (CONTINUED)

Duration of Treatment: All subjects were to receive 4 injections with LAI risperidone (37.5 or 50 mg) administered as 1 injection every 2 weeks into the deltoid muscle.

Patients were allowed to maintain their basic antipsychotic therapy during the entire duration of the study, with the exception of typical depot neuroleptics, and clozapine. Patients were not allowed to take fluoxetine or paroxetine concomitantly.

Criteria for Evaluation:

Pharmacokinetics: Predose plasma concentrations of risperidone, 9-hydroxy-risperidone and the active moiety (risperidone plus 9-hydroxy-risperidone) were determined at Days 1, 15, 29 and 43. Postdose plasma concentrations were determined at Days 50 and 57 (i.e., 7 and 14 days after last study drug administration, respectively).

Tolerability: Primary evaluation - The proportion of subjects who discontinued from the study after having received at least 2 deltoid injections was recorded. A clinically acceptable and positive outcome for the study was if 50% of subjects completed the study among the subjects who received at least 2 i.m. injections with LAI risperidone into the deltoid muscle.

Secondary evaluations - reasons for discontinuation (qualified as related to the deltoid injection site, unrelated to the deltoid injection site, or unknown); subject-rated local site injection pain (measured on a visual analog scale from 0 mm [no pain] to 100 mm [unbearably painful]); investigator-rated local site injection reaction (measured using the injection site evaluation scale for the categories of redness, tenderness, swelling, and induration, rated from 0 to 3 [0 = absent; 1 = mild; 2 = moderate; 3 = severe] for each of the 4 categories).

Safety: Safety was assessed using adverse events (including occurrence of extrapyramidal symptoms as assessed by the Extrapyramidal Symptoms Rating Scale), clinical laboratory tests (hematology, serum chemistry, urinalysis, and pregnancy testing), vital signs, physical examinations, electrocardiograms, and injection site evaluation.

Statistical Methods:

Pharmacokinetics: Plasma concentration data were analyzed using descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation (%CV), median, minimum and maximum. Descriptive statistics were calculated for the actual plasma concentrations of risperidone, 9-hydroxy-risperidone and the active moiety at each visit and after dose-normalization to 50 mg. Data were also presented graphically, to compare the steady-state trough exposure resulting from prestudy gluteal administration with the steady-state trough deltoid exposure.

Tolerability: Primary analysis - The discontinuation rate was analyzed descriptively and a graphical representation over time was generated. The point estimate and 90% CI of the discontinuation rate were calculated.

Secondary analysis - For subjects who discontinued, the reasons for discontinuation (related to the deltoid injection site, unrelated to the deltoid injection site, or unknown) were tabulated and analyzed descriptively. The objective (clinician-rated parameters of local site injection reactions) and subjective (subject-rated local site injection pain on a visual analog scale) local site reactions were tabulated and analyzed descriptively at each time point.

Safety: Safety data were summarized.

SUMMARY - CONCLUSIONS

PHARMACOKINETICS: Steady-state plasma concentrations increased with dose (dose proportionality was not formally assessed). There were no individual subjects with outlying plasma concentrations at Day 50 that would indicate a major early release of active drug from the microspheres.

Descriptive Statistics of the Actual and Dose-Normalized (to 50 mg LAI Risperidone) Plasma Concentration of the Active Moiety Following i.m. Injection of 37.5 or 50 mg LAI Risperidone Into the Deltoid Muscle
(Study RIS-SCH-1008; Pharmacokinetic Analysis Set)

z	Day 1 Predose	Day 15 Predose	Day 29 Predose	Day 43 Predose	Day 50 168 h	Day 57 336 h
37.5 mg LAI Risperidone – Actual Concentrations						
n	32	28	31	25	21	20
Mean (SD)	15.7 (13.4)	17.0 (11.0)	30.9 (19.0)	30.7 (17.2)	24.3 (11.2)	32.7 (19.0)
%CV	85.2	64.6	61.6	56.1	46.0	58.2
Median	9.58	12.8	25.6	26.1	23.0	27.9
Min - Max	2.30-50.6	5.37-47.2	9.13-77.1	11.1-73.6	9.92-61.7	8.20-68.8
37.5 mg LAI Risperidone – Dose-Normalized Concentrations (to 50 mg)						
n	32	28	31	25	21	20
Mean (SD)	21.0 (17.9)	22.6 (14.7)	40.6 (25.6)	40.9 (23.0)	32.4 (14.9)	43.6 (25.4)
%CV	85.2	65.1	63.1	56.1	46.1	58.2
Median	12.8	17.1	32.9	34.8	30.7	37.2
Min - Max	3.07-67.4	5.56–62.9	12.2-103	14.7–98.1	13.2–82.3	10.9–91.7

Continued…

SYNOPSIS (CONTINUED)

Descriptive Statistics of the Actual and Dose-Normalized (to 50 mg LAI Risperidone) Plasma Concentration of the Active Moiety Following i.m. Injection of 37.5 or 50 mg LAI Risperidone Into the Deltoid Muscle (Continued)

50 mg LAI Risperidone						
n	5	6	9	9	7	9
Mean (SD)	16.0 (18.1)	25.4 (18.5)	41.7 (33.9)	38.4 (17.9)	37.6 (25.3)	43.5 (17.5)
%CV	113.3	72.7	81.3	46.6	67.2	40.2
Median	11.5	22.5	40.4	38.3	31.3	42.5
Min - Max	BQL–45.0	BQL–49.0	1.48-118	13.8–64.9	15.2–89.0	21.6–75.5
37.5 and 50 mg LAI Risperidone Combined - Dose-Normalized Concentrations (to 50 mg)						
n	37	34	40	34	28	29
Mean (SD)	20.3 (17.7)	23.1 (15.1)	40.9 (27.2)	40.3 (21.5)	33.7 (17.7)	43.5 (22.9)
%CV	87.4	65.7	66.6	53.4	52.4	52.6
Median	11.9	17.1	33.6	36.7	30.9	37.3
Min - Max	BQL–67.4	BQL–62.9	1.48–118	13.8–98.1	13.2–89.0	10.9-91.7

BQL: below quantification limit.

TOLERABILITY: Fifty-one subjects received at least 2 deltoid injections. Of these, 44 (86%) completed the study.

Tolerability Analysis (Primary) - Discontinuation Rate: Descriptive Statistics (Study RIS-SCH-1008; Subjects Who Received at Least 2 Deltoid Injections)

Subject Completed Treatment/Trial	N	Proportion (%)	90% CI
COMPLETED	44	86.27	(75.76 ; 93.38)
WITHDRAWN	7	13.73	(6.62 ; 24.24)

CI = confidence interval

None of the subjects who discontinued did so due to reasons related to the injection site.

Mean increases in pain from predose to postdose were higher in subjects who had received 50 mg LAI risperidone (approximately 5 to 10 mm) than in those who had received 37.5 mg LAI risperidone (approximately 1 to 3 mm).

At 2 hours after the injection, investigators observed mild injection site reactions (induration, redness, swelling, and/or tenderness) in a maximum of 10 (19%) of 53 subjects. Scores returned to 'absent' at the predose assessment of the next injection 2 weeks later. No clinically relevant differences were observed between subjects who had received 50 mg LAI risperidone and those who had received 37.5 mg LAI risperidone.

SAFETY RESULTS: The adverse events profile in this study was consistent with the previously documented safety profile of LAI risperidone. Twenty-one (approximately 40%) of 53 subjects experienced 1 or more treatment-emergent adverse events. The most common adverse events (occurring in >5% of subjects) were injection site pain, fatigue, and sedation. Two subjects experienced a serious treatment-emergent adverse event (worsening of schizophrenia), both of which were considered by the investigator to be unrelated to study drug. Two subjects discontinued from the study due to treatment-emergent adverse events (sedation and extrapyramidal disorder, both considered by the investigator to be mild and possibly related to study drug). There were no deaths during the study.

There were no appreciable differences in Extrapyramidal Symptoms Rating Scale, laboratory parameters, vital signs, physical examination, electrocardiograms, or injection site evaluations from baseline to study end point.

CONCLUSION: The deltoid injection was well tolerated. Forty-four (86%) of 51 subjects who received at least 2 deltoid injections completed the study. This is a clinically acceptable and positive outcome for the study, based on the predetermined criteria. Additionally, none of the subjects who discontinued did so due to reasons related to the injection site.

Mean scores of subject-rated injection site pain, and investigator-rated injection site reaction increased slightly at 2 hours postdose compared with baseline, and returned to baseline at the predose assessment of the next injection.

Subsequent to the dose increase with the switch from gluteal to deltoid injection site, mean predose plasma concentrations increased to reach a new equilibrium (steady-state) from the third study injection onwards. Plasma concentrations measured on Days 43 to 57 are the result of the deltoid study drug administration only and are consistent with levels after gluteal injection measured in other studies.

Steady-state plasma concentrations of active moiety, risperidone and 9-hydroxy-risperidone resulting from deltoid injection (Day 43 to 57) increased with dose.

LAI risperidone injected into the deltoid muscle was safe and well tolerated. There were no apparent differences in the safety and tolerability of LAI risperidone injected into the deltoid muscle, compared with previously evaluated gluteal injections.

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