SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	To be determined
Name of Active Ingredient(s)	R092670 (paliperidone palmitate)

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Status: Approved

Date: 2 September 2014

Prepared by: Janssen Research & Development, LLC (formerly Johnson & Johnson Pharmaceutical Research and Development [J&JPRD])

Protocol No.: R092670PSY1005

Title of Study: A Single-Dose, Open-Label, Randomized, Parallel-Group Study to Assess the Pharmacokinetics, Safety, and Tolerability of a Paliperidone Palmitate 3-Month Formulation in Subjects With Schizophrenia

EudraCT Number: 2007-003581-17

NCT No.: NCT01559272

Clinical Registry No.: CR012652

Coordinating Investigator(s): David Walling, PhD - CNS Network, LLC, 12772 Valley View St., Suite 3, Garden Grove, CA, USA

Study Center(s):

Panel A: Belgium (2 sites), Bulgaria (1 site), Malaysia (1 site), South Africa (1 site), Taiwan (3 sites), and the USA (10 sites).

Panel B: Belgium (1 site), Bulgaria (1 site), Croatia (1 site), Israel (3 sites), Malaysia (2 sites), Republic of Korea (2 sites), Slovakia (3 sites), South Africa (1 site), Spain (4 sites), Taiwan (3 sites), and the USA (3 sites).

Panel C: Belgium (1 site), Bulgaria (1 site), Malaysia (2 sites), Republic of Korea (2 sites), Spain (1 site), Taiwan (2 sites), and the USA (1 site).

Panel D: Belgium (1 site), Bulgaria (1 site), Croatia (1 site), Israel (2 sites), Malaysia (3 sites), Republic of Korea (2 sites), Slovakia (3 sites), South Africa (1 site), Spain (4 sites), and the USA (2 sites).

Publication (Reference): None

Study Period:

Panel A: Study initiation date: 29 February 2008; Study completion date: 28 October 2009.

Panel B: Study initiation date: 14 April 2010; Study completion date: 11 April 2012.

Panel C: Study initiation date: 04 August 2008; Study completion date: 26 October 2009.

Panel D: Study initiation date: 19 January 2012; Study completion date: 14 May 2014.

Phase of Development: Phase 1

Objectives: The primary objectives of this study were (1) to evaluate the pharmacokinetics (PK), safety, and tolerability of a 3-month injection interval formulation of paliperidone palmitate (F015), [redacted], at a single dose of 300 mg eq. administered in the gluteal muscle in subjects with schizophrenia (Panel A); and (2) to evaluate the PK, safety, and tolerability of single escalating doses of the 3-month injection interval formulation of paliperidone palmitate administered in the gluteal and deltoid muscle in subjects with schizophrenia (Panels B and D).

The secondary objectives were (1) to evaluate the relative bioavailability of the paliperidone palmitate formulations after deltoid and gluteal injection compared with a 1 mg immediate release (IR) formulation of paliperidone; (2) to explore the dose-proportionality of paliperidone palmitate after gluteal and deltoid injection; and (3) to investigate [redacted] n the PK of paliperidone (Panels A and C).

Methodology: This was a multicenter, randomized, open-label, parallel-group study in 4 panels (A, B, C, and D). Each panel comprised of 2 sequential single-dose treatment periods (Period 1 and Period 2).

Number of Subjects (planned and randomized): Planned: Approximately 74 subjects (37 subjects per treatment group) were to be enrolled in the study for Panel A, 125 subjects (25 per treatment group) for Panel B, 25 subjects for Panel C, and 100 subjects (25 per treatment group) for Panel D. Attempts were to be made to enroll at least 1 female for every 4 males enrolled and at least 1 subject in each body mass index (BMI) class (<25, 25 to 30, >30 kg/m²) per treatment group.

Randomized:

Panel A: Seventy-four subjects were randomized in Panel A of the study; however, 72 subejcts received the study agent.

Panel B: One hundred twenty nine subjects were randomized in Panel B of the study; however, 128 subejcts received the study agent.

Panel C: Twenty-five subjects were enrolled in Panel C of the study.

Panel D: One hundred subjects were randomized in Panel D of the study.

A total of 328 subjects were randomized in the 4 panels of the study, of which 325 subjects received the study agent.

Diagnosis and Main Criteria for Inclusion: Males and females, aged between 18 and 65 years, inclusive, who met the diagnostic criteria for schizophrenia or schizoaffective disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), for at least 1 year before screening, with a BMI between 17 and 35 kg/m^2 (inclusive), and a body weight of at least 47 kg, were eligible for enrollment in this study. Subjects who attempted suicide within 12 months before screening, and had a DSM-IV diagnosis of alcohol or substance dependence within 12 months prior to screening, or a DSM-IV diagnosis of substance abuse within 3 months prior to screening, were excluded from the study.

Test Product, Dose and Mode of Administration, Batch No.:

Period 1:

- Panels A and C: 1 mg paliperidone IR solution in the gluteal muscle.
- Panels B and D: 1 mg paliperidone IR solution in the deltoid or gluteal muscle.

Batch numbers and expiry dates: 07F04/F024, 31 May 2008; 08A30/F024, 31 December 2008; 08I23/F024, not used; 10A27/F024, December 2010; and 11K02/F024, November 2012.

Period 2:

All subjects received a long-acting paliperidone palmitate formulation. The 3-month injection interval formulation F015 used in Panels A, B, and D had [redacted] The injection was given in the same muscle but at the opposite side (left or right) as in Period 1. The following study agents were administered in Period 2:

Panel A: a single i.m. injection of 1.5 ml of the following formulations of paliperidone palmitate:

- 200 mg eq./mL F015, [redacted], injected in the gluteal muscle (batch number, expiry date: 07K21/F015, 31 December 2008).
- 200 mg eq./mL F015, [redacted], injected in the gluteal muscle (batch number, expiry date: 07L11/F015, 31 December 2009).

[redacted].

Panel B: a single i.m. injection of 1 of the following doses of paliperidone palmitate:

- 75 mg eq. F015 injected in the gluteal muscle.
- 150 mg eq. F015 injected in the gluteal muscle.
- 450 mg eq. F015 injected in the gluteal muscle.
- 300 mg eq. F015 injected in the deltoid muscle.
- 450 mg eq. F015 injected in the deltoid muscle.

Batch number and expiry date: 10A08/F015, 31 January 2012.

Panel C: a single 1.5 ml i.m. injection of [redacted], injected in the gluteal muscle (batch number, expiry date: 07L04/F016, 31 December 2009).

Panel D: a single i.m. injection of 1 of the following doses of paliperidone palmitate:

- 525 mg eq. F015 injected in the gluteal muscle.
- 525 mg eq. F015 injected in the deltoid muscle.
- 350 mg eq. F015 injected in the gluteal muscle.
- 175 mg eq. F015 injected in the deltoid muscle.

Batch number and expiry date: 11J26/F015, 30 November 2013.

Subjects were to be first enrolled in Panels A and C. Once the interim analyses of these panels were available, subjects then enrolled in Panel B. After the interim analysis of Panel B, Panel D was started to study higher doses, as well as other clinically relevant dose administrations.

Duration of Treatment: For each of the 4 panels, there was a screening phase (up to 21 days before the first study agent administration of the first period) followed by an open-label treatment phase consisting of 2 single-dose treatment periods. The study agent injection was followed by a 96-hour observation period in Period 1, and a 364-day observation period (544-day in Panel D and those who consented in Panel B) in Period 2. Successive study agent administration was separated by a washout period of at least 7 and no more than 21 days. The total study length was from 53 weeks to a maximum of 58 weeks. For Panel D, and if consent was given to the extension period for subjects in Panel B, the study length was increased by approximately an additional 26 weeks.

An interim analysis was conducted after 63 subjects in Panel A completed their Day 196 assessments in Period 2 to evaluate the PK and safety. Recruitment into Panel B was to start only if the F015 formulation exhibited a local tolerability and safety profile that was acceptable and comparable to the 1-month formulation.

Subjects were enrolled in Panel C once enrollment in Panel A was completed. An interim analysis was conducted after 25 subjects completed their Day 196 visit assessments in Panel C.

In Panel B, interim analyses were conducted after a minimum of 15 subjects per treatment group completed their Day 196 assessments in Period 2 and after all subjects per treatment group completed their Day 364 to evaluate the pharmacokinetics and safety.

In Panel D, an interim analysis was conducted after at least 10 subjects who received 525 mg eq. F015 injection (either deltoid or gluteal) completed Day 84 of Period 2 to evaluate the PK and safety. Another interim analysis was conducted when all subjects, assigned to one of the 525 mg-eq. treatments, completed the study (Day 544 of Period 2) and all other subjects completed at least Day 364 of Period 2.

Criteria for Evaluation:

Pharmacokinetics: Serial PK blood samples for determination of paliperidone and/or paliperidone palmitate were collected for a 96-hour observation period in Period 1 and a 364- or 544-day observation period in Period 2. The following key PK parameters were calculated for paliperidone: 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 quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from time 0 to infinite time (AUC_{∞}), half-life ($t_{1/2}$), and relative bioavailability of paliperidone palmitate (F_{rel}). Additional PK parameters were included, if deemed appropriate.

Psychiatric evaluations: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) and Clinical Global Impression-Severity (CGI-S) were assessed, primarily for safety.

Pharmacogenomics: An optional pharmacogenomic blood sample (10 mL) was collected to allow for pharmacogenomic research, as necessary.

Safety: Safety and tolerability were evaluated throughout the study.

The total volume of blood to be drawn for clinical laboratory tests, PK evaluations, and optional pharmacogenomic research was approximately 267 mL.

Statistical Methods:

Sample Size Determination

The primary objective was to document the PK profile of the new formulation. Based on the results from Panel A, a decision was made and a formulation was selected for further assessment. As the aim was to develop a 3-month formulation, the key parameter for Panel A was the $t_{1/2}$. For similar reasons, this was also the key parameter in Panel C.

In Panels B and D, the interest was to document the PK profile and explore exposure for different doses and injection sites. The parameters of interest therefore were AUC and C_{max}.

Panel A: The intersubject coefficient of variation of the apparent $t_{1/2}$ was estimated to be approximately 37% after injection with the [redacted] Assuming an intersubject coefficient of variation of 40% for $t_{1/2}$, a sample size of 20 subjects per treatment group who completed the study was sufficient for the point estimate of the (geometric) mean $t_{1/2}$ for each paliperidone palmitate treatment to fall within 82.9% and 120.6% of the true $t_{1/2}$ with 95% confidence interval (CI).

Panel B: The intersubject coefficient of variation of AUC and C_{max} of paliperidone was estimated to be approximately equal to 50% after injection with [redacted] Assuming an intersubject coefficient of variation of 50% for AUC and C_{max} of paliperidone, a sample size of 14 subjects per treatment group who completed the study was sufficient for the point estimate of the geometric mean AUC and C_{max} to fall within 74.9% and 133.5% of the true value with 95% CI for each paliperidone palmitate treatment.

Panel C: Assuming an intersubject coefficient of variation of 40% for $t_{1/2}$, a sample size of 14 subjects who completed the study was sufficient for the point estimate of the geometric mean $t_{1/2}$ to fall within 79.4% and 126.0% of the true $t_{1/2}$ with 95% CI.

Panel D: Assuming an intersubject coefficient of variation of 50% for AUC and C_{max} of paliperidone, a sample size of 14 subjects per treatment group who completed the study was sufficient for the point estimate of the geometric mean AUC and C_{max} to fall within 74.9% and 133.5% of the true value with 95% CI for each paliperidone palmitate treatment.

Assuming a dropout rate of approximately 45%, 74 subjects in Panel A (37 subjects per treatment group), 125 subjects in Panel B (25 subjects per treatment group), 25 subjects in Panel C, and 100 subjects in Panel D (25 subjects per treatment group) were to be enrolled in the study to ensure that at least 40 subjects (20 subjects per treatment group) in Panel A, 70 subjects (14 subjects per treatment group) in Panel B, 14 subjects in Panel C and 56 subjects (14 subjects per treatment group) in Panel D completed all assigned treatments and assessments on Day 364.

Pharmacokinetics: Descriptive statistics for PK parameters (including arithmetic mean, standard deviation [SD], coefficient of variation, median, minimum, maximum and geometric means) were presented for each treatment.

The parameters of interest for the statistical analysis to evaluate the relative bioavailability of paliperidone palmitate versus 1 mg paliperidone IR after deltoid and gluteal injection were the log-transformed estimated AUCs [AUC_{last}, AUC_{∞}] from Period 1 and Period 2. Data from subjects who completed the study (Period 1 and Period 2) were included in the statistical analysis. If one of the PK parameters of interest was not estimable for a given subject in 1 or more periods, the subject's data was not included in the statistical analysis of that particular PK parameter. For each randomized group, a mixed-effect analysis of variance model that included treatment (paliperidone IR, paliperidone palmitate) as fixed effect, and subject as a random effect, was used to estimate the least squares means and intrasubject variance.

Using these estimated least squares means and intrasubject variance, the point estimate and 90% CIs for the difference in means on a log scale between paliperidone palmitate and 1 mg paliperidone IR was constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean AUCs of paliperidone palmitate versus 1 mg paliperidone IR For this analysis, AUC after paliperidone palmitate were dose-normalized to 1 mg eq. by dividing AUC by the dose received.

To explore dose-proportionality, log-transformed dose-normalized (to the 350 mg eq. dose) PK parameters were plotted versus the dose for each injection site separately. A linear regression model with log-transformed dose-normalized (to the 350 mg eq. dose) PK parameters versus log-transformed dose as a predictor was fitted and used to estimate the corresponding slope with a 95% CI, for each injection site separately. [redacted] Only Panel B and D were included in the analysis.

For the interim analyses, the interim paliperidone plasma concentration-time data was subjected to non-compartmental analysis and population PK analysis using nonlinear mixed effects modeling. Available formulation characteristics were tested as potential covariates affecting PK parameters.

Data collected during the extension period were evaluated and reported.

Psychiatric analysis: Descriptive statistics on raw data and changes from baseline for PANSS and CGI-S are presented by treatment and time point. Interpretation of results is confounded by the fact that all subjects were maintained on other antipsychotic medication throughout the course of the study.

Safety: All subjects who were randomly assigned to a treatment group and received at least 1 dose of the study agent were included in the safety and tolerability analysis. Baseline for all laboratory evaluations, vital signs, 12-lead electrocardiogram (ECG) measurements, and scales was defined as the last evaluation done before study agent administration of each period. Safety was evaluated by examining the incidence and type of adverse events (AEs), extrapyramidal symptoms (EPS) scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], and Simpson and Angus Rating Scale [SAS]), Columbia-Suicide Severity Rating Scale (C-SSRS, Panels B and D), local tolerability (injection site evaluations by the investigator and the subject), and changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the screening phase through study completion, including the washout interval. Interpretation of results is confounded by the fact that all subjects were maintained on other antipsychotic medication throughout the course of the study and only a single dose of the three-month formulation was administered.

RESULTS:

STUDY POPULATION:

Panel A: Seventy-four (74) subjects were randomized in Panel A of the study. Of these, 72 subejcts received the study agent. Of the 72 subjects, 48 subjects (66.7%) completed and 24 subjects (33.3%) withdrew from the study. A majority of the subjects were males (72.2%) and the median age was 43.0 years (range: 22-60 years). Seventy-two subjects (100.0%) received 1 mg i.m. paliperidone IR during Period 1 of Panel A. In Period 2, 35 subjects (89.7% of subjects randomized to this treatment) received [redacted] in the gluteal region and 31 subjects (93.9%) received [redacted] in the gluteal region.

Panel B: A total of 129 subjects were randomized in the 5 treatment groups in Panel B of the study. Of these, 128 subjects received the study agent. Of these 128 subjects, 104 subjects (81.3%) completed Panel B prior to entering the extension, and 24 subjects (18.8%) withdrew from the study. A majority of the subjects were males (58.6%) and the median age was 43.0 years (range: 22-63 years). One hundred twenty-eight subjects (100.0%) received 1 mg i.m. paliperidone IR during Period 1 of Panel B. In Period 2, 23 subjects (92.0%) received 75 mg eq. F015 [redacted] paliperidone palmitate in the gluteal region, 25 subjects (92.6%) received 150 mg eq. F015 [redacted] paliperidone palmitate in the gluteal region, 25 subjects (96.2%) received 300 mg eq. F015 [redacted] paliperidone palmitate in the deltoid region, 22 subjects (88.0%) received 450 mg eq. F015 [redacted] paliperidone palmitate in the gluteal region, and 25 subjects (100.0%) received 450 mg eq. F015 [redacted] paliperidone palmitate in the deltoid region.

Panel C: Twenty-five (25) subjects were enrolled in Panel C of the study. Of these, 22 subjects (88.0%) completed and 3 subjects (12.0%) withdrew from the study. A majority of the subjects were males (72.0%) and the median age was 43.0 years (range: 25-57 years). Twenty-five subjects (100.0%) received 1 mg i.m. paliperidone IR during Period 1 of Panel C. In Period 2, 24 subjects (96.0%) received 150 mg eq. paliperidone palmitate in the gluteal region.

Panel D: One hundred (100) subjects were randomized in Panel D of the study. Of these, 71 subjects (71.0%) completed the study, and 29 subjects (29.0%) withdrew from the study. A majority of the subjects were males (71.0%) and the median age was 41.0 years (range: 21-64 years). One hundred subjects (100.0%) received 1 mg i.m. paliperidone IR during Period 1 of Panel D. In Period 2, 25 subjects (96.2%) received 175 mg eq. F015 [redacted] paliperidone palmitate in the deltoid region, 24 subjects (100.0%) received 350 mg eq. F015 [redacted] paliperidone palmitate in the gluteal region, 25 subjects (100.0%) received 525 mg eq. F015 [redacted] paliperidone palmitate in the gluteal region, and 24 subjects (96.0%) received 525 mg eq. F015 [redacted] paliperidone palmitate in the deltoid region.

Across the four panels, 325 subjects received paliperidone IR and 308 subjects received a single-dose of a three-month formulation (F015 or F016).

PHARMACOKINETIC RESULTS:

Panels A and C

The results in Panels A and C of the paliperidone palmitate injections were compromised by incomplete injections of the study agent in some subjects as a result of inadequate shaking prior to injection. Nevertheless the following conclusions could be drawn:

- In only 3 samples (0.7%) a quantifiable paliperidone palmitate plasma concentration was obtained confirming the robustness of the release of paliperidone palmitate from the F015 and F016 formulations.
- In general, the data supported that the F015 formulation of paliperidone palmitate can be administered in the gluteal or deltoid muscle every 3 months.

Panels B and D

Summary Table of the Key Pharmacokinetic Parameters of Paliperidone after Gluteal Administration of 75 mg eq., 150 mg eq., 350 mg eq., 450 mg eq. and 525 mg eq. Paliperidone Palmitate (F015) in Period 2

(Study R092670PSY1005)

Pharmacokinetics of paliperidone	75 mg eq. Gluteal			150 mg eq. Gluteal			350 mg eq. Gluteal		
Period 2	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	20	10.8	10.1 (1.39-23.3)	18	12.2	8.33 (3.86-57.4)	24	44.0	36.7 (1.37-187)
t_{max}, days	20		29.00 (16.98-113.99)	18		27.51 (8.09-41.00)	24		31.03 (5.00-84.08)
$AUC_{12months}$, ng.h/mL	16	20352	21133 (11666-34464)	13	30662	28412 (14659-49307)	17	86132	82199 (42606-138011)
$AUC_{18months}$, ng.h/mL	14	21342	21577 (13047-34616)	10	35154	36811 (20711-49307)	17	92922	94811 (45523-138572)
AUC_{∞}, ng.h/mL	16	22007	22214 (10671-34683)	10	39323	42963 (26283-49399)	16	101244	102894 (47481-157706)
$t_{1/2}$, days	18	83.0	44.9 (26.9-341.5)	10	96.6	79.6 (27.7-198.9)	19	94.7	77.4 (22.8-274.1)
$F_{rel, AUC\infty}$, %	13	113.92	117.65 (68.20-137.61)	10	104.37	103.33 (40.64-151.63)	16	118.93	115.91 (77.22-174.74)

Pharmacokinetics of paliperidone	450 mg eq. Gluteal			525 mg eq. Gluteal		
Period 2	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	21	40.3	35.0 (7.31-80.7)	24	63.8	56.3 (11.1-143)
t_{max}, days	21		28.00 (13.00-54.98)	24		23.01 (2.00-41.00)
$AUC_{12months}$, ng.h/mL	20	92597	93608 (34078-154371)	23	123752	113091 (47244-276295)
$AUC_{18months}$, ng.h/mL	17	107055	110699 (54659-186494)	20	131102	112913 (57075-282608)
AUC_{∞}, ng.h/mL	13	115241	123273 (35579-159235	18	145611	142201 (77446-285761)
$t_{1/2}$, days	15	120.5	81.5 (21.2-349.5)	20	91.8	68.5 (29.0-254.4)
$F_{rel, AUC\infty}$, %	11	109.36	111.61 (78.67-138.06)	18	107.80	107.41 (56.51-164.27)

Summary Table of the Key Pharmacokinetic Parameters of Paliperidone after Deltoid Administration of 175 mg eq. 300 mg eq. 450 mg eq. and 525 mg eq. Paliperidone Palmitate (F015) in Period 2

(Study R092670PSY1005)

Pharmacokinetics of paliperidone	175 mg eq. Deltoid			300 mg eq. Deltoid			450 mg eq. Deltoid		
Period 2	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)	N	Mean	Median (Min-Max)
C_{max}, ng/mL	25	25.8	21.2 (9.85-67.3)	20	32.4	28.0 (11.7-69.4)	22	45.0	40.1 (6.49-113)
t_{max}, days	25		23.99(5.00-56.10)	20		34.00 (13.00-83.12)	22		23.98 (12.99-51.07)
$AUC_{12months}$, ng.h/mL	18	49993	44149 (26712-99648)	17	72959	74065 (45401-106437)	19	119012	122682 (22679-216062)
$AUC_{18months}$, ng.h/mL	14	46806	45391 (26712-70029)	12	75884	76193 (49856-117544)	16	132017	138021 (34360-216062)
AUC_{∞}, ng.h/mL	22	50407	46480 (26773-100550)	17	78166	77925 (50607-112132)	17	132645	131651 (64417-216177)
$t_{1/2}$, days	22	56.6	51.7 (19.7-143.1)	17	77.7	73.5 (28.3-177.8)	18	85.9	71.8 (24.5-226.5)
$F_{rel, AUC\infty}$, %	22	108.77	107.94 (74.85-149.89)	15	106.61	102.60 (77.70-136.12)	14	108.43	101.78 (81.84-145.99)

Pharmacokinetics of paliperidone	525 mg eq. Deltoid		
Period 2	N	Mean	Median (Min-Max)
C_{max}, ng/mL	24	80.0	57.9 (27.6-416)
t_{max}, days	24		24.51 (0.99-54.99)
$AUC_{12months}$, ng.h/mL	20	136074	124735 (85817-221565)
$AUC_{18months}$, ng.h/mL	18	141127	125429 (85817-244079)
AUC_{∞}, ng.h/mL	22	144173	128969 (85887-257003)
$t_{1/2}$, days	22	60.7	56.9 (21.3-115.2)
$F_{rel, AUC\infty}$, %	20	112.72	109.98 (84.83-144.77)

- After i.m. injection of 75-525 mg-eq. paliperidone palmitate (F015) in the gluteal or deltoid muscle, paliperidone palmitate is slowly absorbed, reflected by a T_{max} of approximately 23 to 34 days and an apparent half-life of approximately 2-4 months; the half-life was similar in the gluteal and deltoid dose groups, except for the 75 mg eq. gluteal dose group where the half-life was slightly lower compared to the other dose groups.These data support the dosing of paliperidone palmitate every 3 months.
- The median apparent half-life of paliperidone palmitate is approximately 44.9 days for a dose of 75 mg eq., 79.6 days for 150 mg eq., 77.4 days for 350 mg eq., 81.5 days for 450 mg eq. and 68.5 days for 525 mg eq. after a single dose in the gluteal muscle and 51.7 days for 175 mg eq., 73.5 days for 300 mg eq., 71.8 for 450 mg eq. and 56.9 days for 525 mg eq. after a single dose in the deltoid muscle.
- The median dose-normalized C_{max}, AUC_{∞} was similar for all doses. Additionally, both the paliperidone AUC_{∞} and C_{max} increased dose-proportionally in the 75-525 mg eq. range according to the statistical analysis.
- The LSmeans C_{max} of paliperidone was higher after injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (27% increase over all dose levels) whereas there was no difference between both injection sites for AUC_{∞}.
- After injection of paliperidone palmitate (F015) the paliperidone AUC_{∞} and C_{max} were independent of BMI, or race. Exposure (Median C_{max}) was slightly higher in males after single dose administration.
- The relative bioavailability approximated 100%, independent of dose, injection site, BMI, race or gender.
- The estimated inter-subject variability (coefficient of variation, %CV) for the AUC_{∞} and C_{max} varied between 22.0 and 34.8 and 49.1 and 99.2, respectively, for the different treatment groups.
- Paliperidone is a racemic mixture. The R078543(+)/R078544(-) PK parameter ratios after i.m. injections of paliperidone palmitate are approximately 1.8 and 1.9 for AUC ($AUC_{12months}$ and AUC_{∞}) and C_{max} respectively, similar to the 1-month formulation.
- After i.m. administration of paliperidone palmitate, a low incidence of low paliperidone palmitate concentrations was observed, similar to the 1-month formulation.
- With increased training of trial personnel prior to the initiation of Panel B and Panel D, there were no issues related to incomplete injection of the study agent due to incomplete shaking, as observed in Panels A and C.

PHARMACOGENOMIC RESULTS:

- Pharmacogenomic analyses from the genetic samples collected in this study have not been conducted and may be reported separately, if warranted.

PSYCHIATRIC RESULTS:

In Panels A, B, C, and D, no clinically significant changes were seen in the mean PANSS total or factor scores between baseline of Period 1 and endpoint with the end of study scores being within 3 points of the baseline score. This was expected since patients were treated throughout the course of the study with oral antipsychotic medication and required stable symptoms for study entry. Across panels, the median CGI-S score was 3 indicating mild illness and remained at 3 for all groups and all of the panels.

SAFETY RESULTS:

It should be noted that causality assessment for many AEs (except injection site reactions) is difficult due to subjects continuing oral antipsychotic and other medications throughout the trial. Paliperidone palmitate was well tolerated at doses up to 525 mg eq./mL.

The most commonly reported treatment-emergent adverse events (TEAEs) were headache and insomnia (each in 5.6% subjects) in Period 1; and headache and nasopharyngitis (each in 13.6% subjects), and toothache (6.1%) in Period 2 of Panel A; headache (4.7%), anxiety and constipation (each in 3.1% subjects) in Period 1; and nasopharyngitis (12.5%), headache (11.7%), anxiety (10.0%), insomnia, diarrhea, toothache and weight increased (each in 7.5% subjects), abdominal pain and back pain (each in 6.7% subjects), weight decreased and tachycardia (each in 5.8% subjects), and depression, psychotic disorder and schizophrenia (each in 5% subjects) in Period 2 of Panel B; headache (8.0%) in Period 1; and upper respiratory tract infection (25.0%), headache (16.7%), constipation (12.5%), vomiting, dystonia, injection site warmth, back pain and diabetes mellitus (each in 8.3% subjects) in Period 2 of Panel C; and insomnia (3.0%) in Period 1; and nasopharyngitis (10.2%), headache (7.1%), back pain (6.1%), dizziness and weight increased (each in 5.1% subjects) in Period 2 of Panel D.

No deaths occurred in Panels A, C, and D of the study. One death occurred during Panel B, which was due to the serious adverse event (SAE) of metastatic melanoma. One or more treatment-emergent SAEs were reported in 9 subjects in Panel A, 14 subjects in Panel B, 1 subject in Panel C, and 11 subjects in Panel D. The majority of the SAEs were in the psychiatric disorders system organ class (SOC). Three subjects withdrew from Panel A due to TEAEs of anxiety, suicidal ideation, and hypertension, 3 subjects withdrew from Panel B due to TEAEs of psychotic disorder, metastatic malignant melanoma, muscle spasticity and dysphemia (each reported in 1 subject), and 1 subject withdrew from Panel D due to TEAE of of psychotic disorder. No subjects withdrew from Panel C of the study due to TEAEs. No clinically relevant changes in any of the hematology, chemistry, and urinalysis parameters evaluated were observed in any of the 4 panels. No notable changes from baseline over time in any of the vital sign parameters were observed in any of the 4 panels.

Across the four panels, the majority of the subjects had normal ECG values of heart rate (HR) and PR, QRS, and RR intervals and no clinically relevant mean changes from baseline to EOS/early withdrawal were observed for a majority of the ECG parameters. In Panel A during Period 2, no subjects had a QT interval corrected by the method of Fridericia (QTcF) value >480 msec in either treatment group. In Panel B during Period 2, 1 subject in the 300 mg eq. F015 [redacted] paliperidone palmitate in the deltoid region treatment group had a QTcF >500 msec (occurring at Day 140). In Panel C during Period 2, no subjects had a QTcF value >480 msec. In Panel D, during Period 2, 1 subject in the 525 mg eq. F015 [redacted] paliperidone palmitate in the gluteal region treatment group had a QTcF >480 msec and <500 msec (Day 224).

No clinically meaningful change in the AIMS, BARS, and SAS scores from baseline to the end of the study was observed in any of the 4 panels.

Paliperidone palmitate was well tolerated at the site of injection at all doses tested in all the four panels.

- In Panel A, 6 subjects (1 subject in the 1 mg i.m. paliperidone IR treatment group, 2 subjects in the [redacted] in the gluteal region group, 3 subjects in the [redacted] in the gluteal region group) had TEAEs related to injection site reactions (pain, irritation, or rash).
- In Panel B, 10 subjects (1 subject in the 1 mg i.m. paliperidone IR treatment group, 1 subject in the 150 mg eq. F015 [redacted] paliperidone palmitate in the gluteal region treatment group, 3 subjects in the 300 mg eq. F015 [redacted] paliperidone palmitate in the deltoid region treatment group, and 5 subjects in the 450 mg eq. F015 [redacted] paliperidone palmitate in the deltoid region treatment group) had TEAEs related to injection site reactions (mass, pruritus, pain, induration, illness, erythema, or swelling).

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Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.

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