EXAMPLE 2	PI-75
Evaluation of the Pharmacokinetic Profile of Gluteal Versus Deltoid Intramuscular Injections of Paliperidone Palmitate 100 mg Equivalent in Patients with Schizophrenia	EVALUATION OF THE PHARMACOKINETIC PROFILE OF GLUTEAL VERSUS DELTOID INTRAMUSCULAR INJECTIONS OF PALIPERIDONE PALMITATE 100 MG EQUIVALENT IN PATIENTS WITH SCHIZOPHRENIA. A. Cleton,[1] S. Rossenu,[1] D. Hough,[2] H. Crauwels,[1] A. Vandebosch,[1] J. Berwaerts,[2] M. Eerdekens,[1] I. Francetic[3]; [1]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium, [2]Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ, [3] Institute of Clinical Pharmacology, Clinical Hospital Centre, Zagreb, Croatia
This study was performed to characterize and compare the pharmacokinetic profile of paliperidone palmitate (formulated as described above) following four intramuscular injections in the deltoid or gluteal muscle.	**BACKGROUND**: The aim of this study was to compare the PK profile of paliperidone palmitate 100 mg eq. administered into the deltoid (n=24) or gluteal muscle (n=25).
Method In this multiple-dose, open-label, parallel-group study, patients with schizophrenia were randomized to receive four consecutive intramuscular injections (days 1, 8, 36 and 64) of paliperidone palmitate 100 mg-eq. administered into either the deltoid (n=24) or gluteal muscle (n=25). Plasma samples for pharmacokinetic analyses were collected. The total paliperidone concentration was calculated as the sum of both enantiomers.	**METHODS**: In this multiple-dose, open-label, parallel-group study, patients with schizophrenia were randomized to receive 4 consecutive injections (Days 1, 8, 36 and 64).

Results	**RESULTS**:
The median C_{max} for paliperidone was higher in the deltoid versus the gluteal muscle after the second (31.3 versus 24.1 ng/mL) and fourth (23.7 versus 22.3 ng/mL) injections.	The median C_{max} was higher in deltoid vs. gluteal muscle after the 2nd (31.3 vs. 24.1 ng/mL) and 4th (23.7 vs. 22.3 ng/mL) injections.
After four injections, median AUC_{∞} was similar for both injection sites; C_{max} and AUC_{τ} for paliperidone were 30% (90% CI = 100.56 % - 168.93 %) and 20% (90% CI = 93.09 % - 154.69 %) higher in deltoid versus gluteal muscle, respectively.	After 4 injections, the median fluctuation index (FI) was higher (71.9 vs. 56.2%), with a larger intersubject variability for deltoid vs. gluteal injection.
Median T_{max} was similar between injection sites after the second (10 day versus 10 day) and fourth injections (5 versus 6.5 days).	Median T_{max} was similar between injection sites after the 2nd (10 vs. 10 days) and 4th injections (5 vs. 6.5 days). The median concentration-time profile was higher following deltoid injection.
After four injections, the median peak-to-trough ratio was higher (2.3 versus 1.9), with a larger intersubject variability for deltoid versus gluteal injection.	After 4 injections, median AUC_{∞} was similar for both injection sites; C_{max} and AUCτ for paliperidone were 30% (90%CI=100.56-168.93) and 20% (90%CI=93.09-154.69) higher in deltoid vs. gluteal muscle, respectively.
An increase in median predose plasma concentration between days 8, 36 and 64 for both sites suggested subjects were not completely at steady state after four injections. Relative exposure after the fourth injection was slightly lower than after the second injection in both the deltoid and gluteal muscle.	Increased median predose plasma concentrations on Days 8, 36 and 64 suggested subjects were not completely at steady state after 4 injections.
Most commonly reported adverse events (combined injection sites) were orthostatic hypotension (24%), hypotension (14%), diastolic hypotension (12%) and injection site pain (14%). There were four serious adverse events (worsening of psychosis) that led to discontinuations. There were no deaths in the study.	Most commonly reported adverse events (combined injection sites) were orthostatic hypotension (24%), hypotension (14%), diastolic hypertension (12%) and injection site pain (14%). Four patients discontinued due to psychosis.

Paliperidone palmitate was well tolerated with more favorable local tolerability profile in the gluteal versus deltoid; mean injection site pain VSA score was 3.3 for gluteal versus 10.8 for deltoid muscle (day 1, 8 hours after injection.	Paliperidone palmitate was well tolerated, with a mean injection site pain VAS score of 3.3 for gluteal vs. 10.8 for deltoid muscle (Day 1, 8 hours after injection).
Conclusion Paliperidone palmitate 100 mg-eq. injections resulted in an increased AUC_{τ} higher C_{max}, greater FI, but similar T_{max} following four consecutive injections into the deltoid versus gluteal muscle.	**CONCLUSION**: Paliperidone palmitate 100 mg-eq., had an increased AUCτ, higher C_{max} and greater FI when injected into the deltoid vs. gluteal muscle, although similar T_{max} was noted, for both injection sites.
Paliperidone palmitate 100 mg-eq. was systemically and locally well tolerated in this study.	Paliperidone palmitate 100 mg-eq. was well tolerated.

EXAMPLE 3	PI-74
Assessment of the Dose Proportionality of Paliperidone Palmitate 25, 50, 100, and 150 mg eq. Following Administration in the Deltoid or Gluteal Muscles	ASSESSMENT OF THE DOSE PROPORTIONALITY OF PALIPERIDONE PALMITATE 25, 50, 100 AND 150 MG EQ., A NEW LONG-ACTING INJECTABLE ANTIPSYCHOTIC FOLLOWING ADMINISTRATION IN THE DELTOID OR GLUTEAL MUSCLES. A. Cleton,[1] S. Rossenu,[1] D. Hough,[2] H. Crauwels,[1] J. Berwaerts,[2] S. Gopal,[2] A. Vandebosch,[1] C. Rosso Fernandez[3]; [1]Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium, [2]Johnson & Johnson Pharmaceutical Research & Development, Titusville, NJ, [3] Clinical Trial Unit, University Hospital of Bellvitge, Barcelona, Spain
This study evaluated dose proportionality of paliperidone palmitate injections when administered into either the gluteal or deltoid muscle.	**BACKGROUND**: Study evaluated dose proportionality of paliperidone palmitate injections administered in either gluteal or deltoid muscle.
Method A single-dose, open label, parallel-group study of 201 randomized schizophrenia subjects was performed. The subjects were assigned into eight treatment groups: paliperidone palmitate 25 (n=48), 50 (n=50), 100 (n=51) or 150 (n=52) mg-eq. injected into either the deltoid or gluteal muscle. Serial plasma samples were collected for pharmacokinetic evaluation over 126-day period. The total paliperidone concentration was calculated as the sum of both enantiomers.	**METHODS**: A single-dose, open-label, parallel-group study randomized 201 schizophrenia subjects (safety set) into eight treatment groups: paliperidone palmitate 25 (n=48), 50 (n=50), 100 (n=51) or 150 (n=52) mg-eq. injected into deltoid or gluteal muscle.

Dose proportionality was assessed by linear regression model, for each injection site, with log-transformed dose-normalized AUC_{∞} and C_{max} as dependent variables and log-transformed dose as predictor, respectively of C_{max} and AUC_{∞} ratios of the enantiomers were documented.	Paliperidone dose proportionality was assessed by a linear regression model, for each injection site, with log-transformed dose-normalized AUC_{∞} and C_{max} as dependent variables and log-transformed dose as predictor, respectively. C_{max} and AUC_{∞} ratios of enantiomers [R078543(+)/R078544(-)] were documented.
Results Slopes for log-transformed dose-normalized AUC_{∞} were not significantly different from zero for deltoid (slope -0.06; p=0.036) and gluteal injections (slope -0.02; p=0.760 indicating a dose-proportional increase in AUC_{∞}, T_{max}, was comparable between doses but slightly earlier for deltoid (13-14 days) versus gluteal injections (13-17 days). Median C_{max} was higher with deltoid (range 5.3-11.0 ng/mL) versus gluteal (range 5.1-8.7 ng/mL) injections except for the 100 mg-eq. deltoid (slope −0.22, p=0.0062) and gluteal (slope -0.31; p<0.0001) injections, indicating a less than dose-proportional increase in C_{max}. Results of C_{max} and AUC were confirmed using pairwise comparisons. Plasma concentrations of (+)-enantiomer were consistently higher than (−)-enantiomer; (+)/(−) plasma concentrations ratio was approximately 2.4 shortly after administration and decreased to ~1.7 for both injection sites, independent of dose. After a single dose of paliperidone palmitate, subjects received concomitant oral antipsychotics. Treatment-emergent AEs (TEAs) included tachycardia (10%), headache (7%), schizophrenia (6%), insomnia (5%). Only 2% of subjects discontinued due to TEAs. No deaths were reported.	**RESULTS**: AUC_{∞} slopes were not significantly different from zero for deltoid (slope -0.06; p=0.36) and gluteal injections (slope -0.02; p=0.76) indicating dose proportional increase in AUC_{∞}, T_{max} was comparable for doses but slightly earlier for deltoid (13-14 d) vs gluteal injections (13-17 d). Median C_{max} (range 5.1-11.0ng/mL) was higher with deltoid vs gluteal injections except for 100 mg eq. dose. C_{max} slopes were significantly different from zero for deltoid (slope -0.22, p=0.0062) and gluteal (slope -0.31; p<0.0001) injections, indicating a less than proportional increase in C_{max} with dose. Median (+)/(-) C_{max} and AUC_{∞} ratios were ~1.7. After a single dose of paliperidone palmitate, subjects received concomitant oral antipsychotics. Treatment-emergent AEs (TEAEs) included tachycardia (10%), headache (7%), schizophrenia (6%), insomnia (5%), weight gain (5%). Only 2% of subjects discontinued due to TEAEs.

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