CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-264

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDAs	22264
Submission Dates	03 February 2009
Brand Name	INVEGA SUSTENNA ™
Generic Name	(25mg, 50, 75, 100, 150 mg paliperidone) Paliperidone Palmitate (b) (4)
Reviewer	Hao Zhu, Ph.D.
	Kofi Kumi, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Clinical Pharmacology Team Leader	Raman Baweja, Ph.D.
OCP Division	DCP1 (HFD-860)
OND Division	DPP (HFD-130)
Sponsor	Johnson & Johnson R&D, L.L.C.
Submission Type	

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1 EXECUTIVE SUMMARY

Paliperdione has been marked as an extended release (ER) formulation with a once-daily administration schedule for the treatment of schizophrenia. Paliperidone palmitate (b) (4) was originally submitted by Johnson & Johnson Pharmacetucial Research and Development (J&JPRD) on 25 October 2007. On 25 August 2008, the division issued a complete response letter. Following the complete response letter, the discussion meetings between the sponsor and the FDA were held on 9 September 2008 and 21 November 2008. J&JPRD filed the resubmission on 03 February 2009 to address the comments and questions raised by the division in the complete response letter.

In the resubmission package, the sponsor included a recently completed clinical study report (R092670-PSY-3007) to support the initial and maintenance dose of 150 mg eq. An interim analysis of safety data from Study R092670-PSY-1008, a long-term (up to 53 weeks), open-label, safety study, was also provided to support the use of a higher initiation and maintenance dose.

The sponsor proposed dosing regimen was summarized in Table 1. The sponsor's proposal was based on the findings from the recently finished clinical trials and the population PK simulation studies.

Table 1 Summary of the Sponsor Proposed Dosing Regimen

Patient Population	Initial Dosing	Dosing Window	Maintenance Dosing	Dosing Window
(b) (4)				

Our findings, based on the independent simulation studies, were summarized below.

- The sponsor proposed target maintenance dose is 75 mg eq. q 4 weeks and can be adjusted between 25 to 150 mg eq q 4 weeks. The recommended maintenance dosing regimen is acceptable.
    - Paliperidone once daily ER formulation has been approved for the treatment of schizophrenia. The recommended dosing is 6 mg q 24 hour and can be adjusted between 3 mg to 12 mg q 24 hour.

- The simulation showed that 75 mg eq q 4 week using long acting injection yields similar exposure as 6 mg q 24 hour for the ER formulation.
- The simulation also indicated that 25 and 150 mg eq q 4 weeks using long acting injection yields similar exposure as 2 mg q 24 hour and 12 mg q 24 hour for the ER formulation. In the current submission, 25 mg eq q 4 weeks has shown to be effective in treating patients with schizophrenia.

- The sponsor also proposed an initial dose of 150 mg eq on the first day, followed by 100 mg eq by the end of the first week. The proposed initial dosing regimen is acceptable.
  - The desirable exposure is defined as median exposure between the steady state peak and trough concentration following 6 mg q.d. oral ER formulation.
  - Starting the treatment with 150 mg eq dose provides the benefit that the desirable exposure can be achieved within 1 week. Following the proposed initial dosing regimen, the peak exposure is below the highest clinical tested exposure that appears to be safe and well tolerated.

- The sponsor proposed that the second initial dose can be administered within 2 days prior to or after the scheduled time. In addition, the maintenance dose can be given within 1 week prior to or after the scheduled time. The simulation results demonstrated that paliperidone exposure is within the desirable exposure. Therefore the proposed dosing window is acceptable.

- The sponsor proposed an initial dose of 100 mg eq and 75 mg eq on day1 and one week later in combination with a maintenance dose of 50 mg eq for patients with mild renal impairment. The simulation results indicated that paliperidone exposure is mainly within the desirable exposure range. The peak exposure is below the highest clinical tested exposure that appears to be safe and well tolerated. Therefore, the proposed dosing regimen in patients with mild renal impairment is acceptable. It is to note that paliperidone palimtate is not recommended in patients with moderate or severe renal impairment.

- (b) (4)

- (b) (4)

(b) (4)

- We have the following proposals for patients who intend to switch from other long acting injection to paliperidone palimtate long acting injection.

    - One proposal is to use paliperidone ER formulation between the two long acting injections. This would allow the physician to titrate paliperidone dose to compensate the elimination of the previous antipsychotic drug based on the clinical response and also provide a flexible regimen to adjust the dose timely for adverse events. After the patient is stabilized on paliperidone ER formulation and most of the previous antipsychotic drug is eliminated, the paliperidone palmitate injection can be started with the standard initiation dosing.

    - For patients that cannot follow the proposed switching strategy, the alternative proposal is to switch the patients to the maintenance dosing of paliperidone palmitate long acting injection without the loading dose. However, the appropriate maintenance dose will be determined by the physician's clinical judgment and cannot be established by using pharmacokinetic simulation alone.

- The sponsor proposed a re-initiation dosing regimen (Table 1). We found that the re-initiation dosing regimens for patients who miss doses for 4 - 6 weeks and > 6 months are acceptable with the assumption that paliperidone tolerability and the underlying disease progression are not affected due to the missing doses. (b) (4)

- We recommend the re-initiation dose (doses on day 1 and day 8) for a patient who discontinues paliperidone palmitate treatment for 6 weeks – 6 months be the same dose as the previous maintenance dose with a maximum of 100 mg eq.

In addition, we reviewed the sponsor submitted analysis assay validation report. We found that the analytical method used to determine paliperidone concentrations in the plasma is acceptable.

4.1 Recommendations

The Office of Clinical Pharmacology has found this sNDA to be acceptable provided that satisfactory agreement is reached between the sponsor and the division regarding the language in the package insert (PI) and patient prescription information (PPI). Recommendations for consideration for the final labeling are included in the Labeling Section (Section 3) of the review.

4.2 Phase 4 Commitments

None.

_____
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_____
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2 QUESTION BASED REVIEW

Please refer to the pharmacomtrics review Section 1.1 in the appendix 4.1.

3 LABELING RECOMMENDATIONS

Please refer to the pharmacomtrics review Section 1.3 in the appendix 4.1.

4 APPENDICES

4.1 Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is the sponsor proposed initial and maintenance dosing regimen justified?

In the current submission, the sponsor proposed a different initial and maintenance dosing regimen from its original submission (Table 1). The proposed dosing regimen was not completely investigated in the clinical trials (Table 2). Our simulation indicated that the proposed dosing regimen is acceptable.

Evaluation of the maintenance dosing regimen

The sponsor indicated that the target maintenance dose is 75 mg eq. q 4 weeks and can be adjusted between 25 to 150 mg eq q 4 weeks. Paliperidone ER oral formulation has been approved for the treatment of schizophrenia. The recommended maintenance dosing for the ER oral formulation is 6 mg q 24 hours. The simulation showed that 75 mg eq q 4 week using long-acting injection yields similar exposure as 6 mg q 24 hours for the ER injection. Likewise, the exposure following 150 mg and 25 mg eq. q 4 weeks from the long acting injection is similar to the approved 12 mg q 24 hours and 2 mg q 24 hours dosing for the ER oral formulation (Figure 1). Therefore, the sponsor proposed maintenance dose appears to be reasonable.

Evaluation of the initial dosing regimen

The sponsor also proposed an initial dose of 150 mg eq on the first day, followed by 100 mg eq by the end of the first week of the treatment. We evaluated the sponsor proposed initial dosing in two different scenarios.

In the first scenario, patients who have been receiving a different antipsychotic treatment (non-long acting injection) other than paliperidone need to switch to paliperidone long acting injection. The initial paliperidone concentration is zero before the long acting injection is administered. Using 150 mg as the initial dose, the desirable exposure (i.e. median exposure between the steady state peak and trough concentration following 6 mg q.24 hours of oral ER formulation) can be achieved within the first week of the treatment. Whereas using 100 mg and 75 mg as the starting dose, the describable exposure cannot be achieved until 1.5 – 2 weeks later.

In the second scenario, a patient receiving paliperidone ER formulation is switched to paliperidone long-acting injection. The paliperidone initial concentration is assumed to be equivalent to the median steady state trough concentration by the time paliperidone long acting injection is given. As shown in Figure 2 B, the exposure in the first week of the treatment using the initial dose of 75 mg and 100 mg decreases from the desirable concentration range and cannot return until 1.5-2 weeks later. Paliperidone exposure returns to the desirable range in less than 1 week following the initial dose of 150 mg.

In addition, using the proposed initial dosing, the peak exposures under the two simulated scenarios were below the highest exposure tested in the Study R092670-PSY-3007 (i.e. 150 mg administered on the first day and by the end of the first week), which was administered to about 160 subjects and appears to be safe and well tolerated [Please refer to the medical officer: Dr. Jing Zhang's review].

In summary, starting the treatment with 150 mg eq dose provides the benefit to reach the desirable exposure within 1 week. Following the proposed initial dosing regimen, the peak exposure is below the clinical tested exposure that appears to be safe and well tolerated. Therefore, the sponsor proposed initial dosing regimen is reasonable.

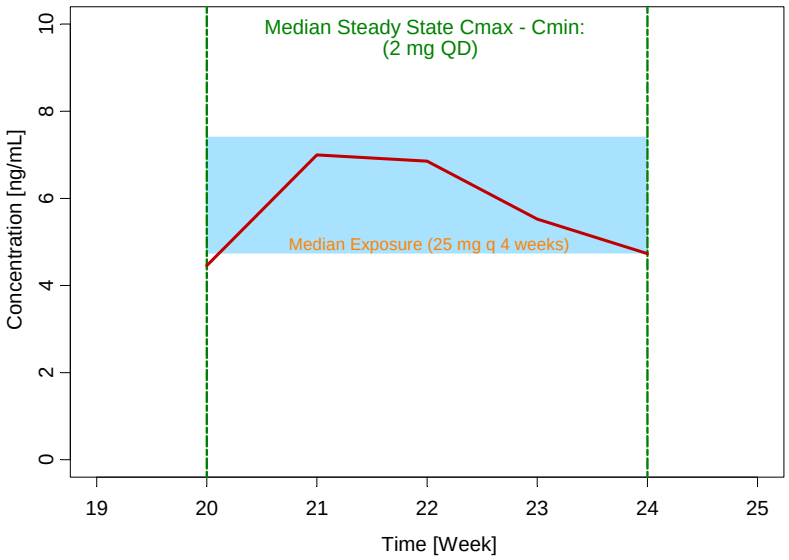
Table 1 Summary of the Proposed Initial and Maintenance Dosing Regimen

Initial Dosing: Injection Site: Detoid Muscle				Maintenance Dosing: Injection Site: Detoid or Gluteal Muscle		Date	Document Type
Dose1 (mg eq)	Time1 (Day)	Dose2 (mg eq)	Time 2 (Day)	Dose (mg eq)	Time		
100	1	100	8	25 - 100	Monthly	25-Oct-07	Original Submission
75-100	1	75 - 100	8	25 - 100	Monthly	9-Sep-08	CR Letter
150	1	100	8	75 (25 - 150)	Monthly	3-Feb-09	Resubmission

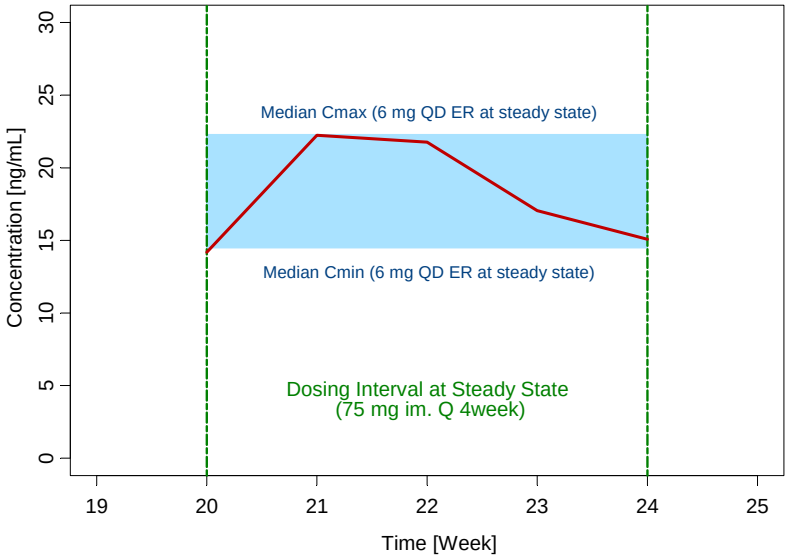
Table 2 Initial and Maintenance Doses being Investigated in the Clinical Trials

Dose Evaluated				Clinical Trial	Document	Date
Initial (mg eq)	Time (Day)	Maintenance (mg eq)	Time (Day)			
150	1	25, 100, 150	8, 36, 64	R092670-PSY-3007	Resubmission	3-Feb-09
None	None	50, 100, 150	1, 8, 36, 64	R092670-PSY-3003	Original Submission	25-Oct-07
None	None	25, 50, 100	1, 8, 36, 64	R092670-PSY-3004	Original Submission	25-Oct-07

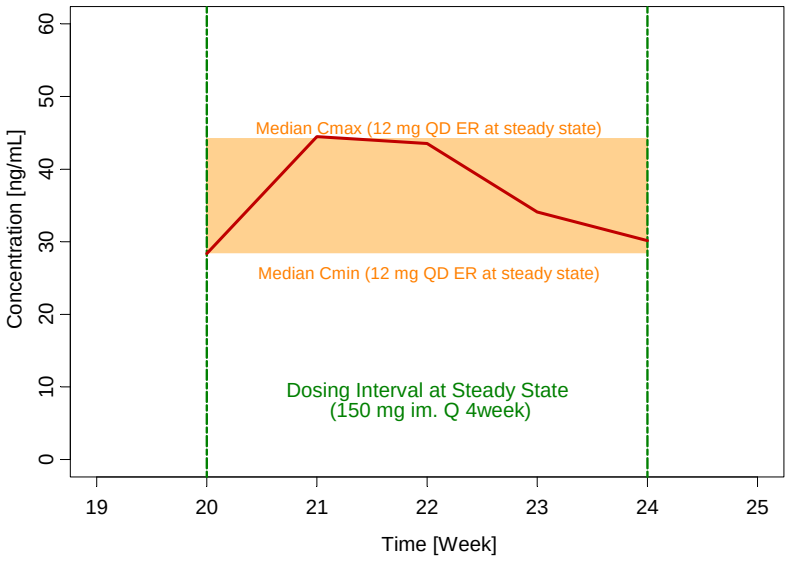
Figure 1 the Simulated Median Exposure following 25 mg (A), 75 mg (B), 150 mg (C) of Long-Acting Injection (Q 4 Weeks) versus the Observed Median Exposure Following 2 mg, 6 mg, and 12 mg (Q24 hour) ER Formulation



(A)



(B)



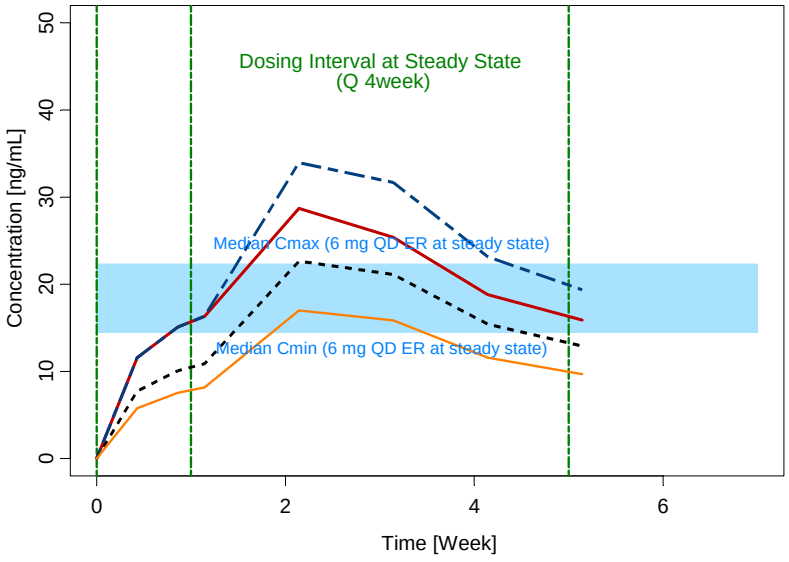
(C)

Note: red line= Model predicted steady state median exposure following 25, 75, 150 mg i m. injection every 4 weeks.

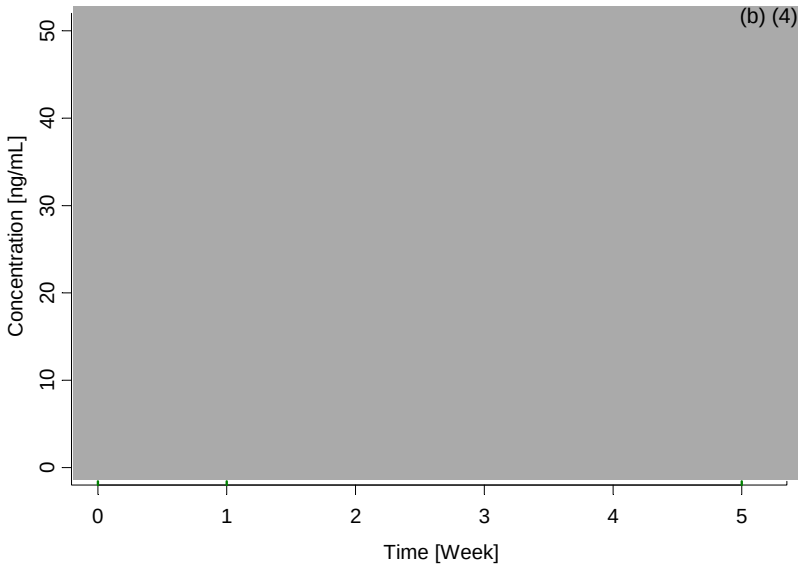
Source:

1. Median Cmax and Cmin at steady state following 6 mg and 12 mg dose once every 24 hours (Obtained from Attachment 2.23 in CSR R092670-SCH-01, P-1051 and P-1048).
2. Median Cmax and Cmin at steady state following 2 mg once daily dosing was derived from the 6 mg and 12 mg q 24 hr data based on the linear PK feature of paliperidone.

Figure 2 Evaluation of Initial Dosing Regimen



(A)



(B)

Note:

A = A patient switches from a different antipsychotic formulation (non-long acting injection) other than paliperidone ER oral formulation to paliperidone long acting injection.

1.1.2 Is the sponsor proposed dosing window justified?

In clinical practice, patients might not be able to receive the paliperidone palmitate injection exactly following the scheduled time. Therefore, the sponsor proposed a dosing window to guide the medical caregiver (Table 3). Our simulations indicated that the sponsor proposed dosing window is acceptable.

The first simulation was to identify the dosing window for the second initial dose. The simulation compared the paliperidone pharmacokinetic profiles when it is given within 2 days prior to and after the scheduled dosing time. The simulation assumes paileridone initial concentration is zero, because the pharmacokinetic profile of the second dose is the primary focus. Even when the initial paliperidone concentration is not zero, the residual

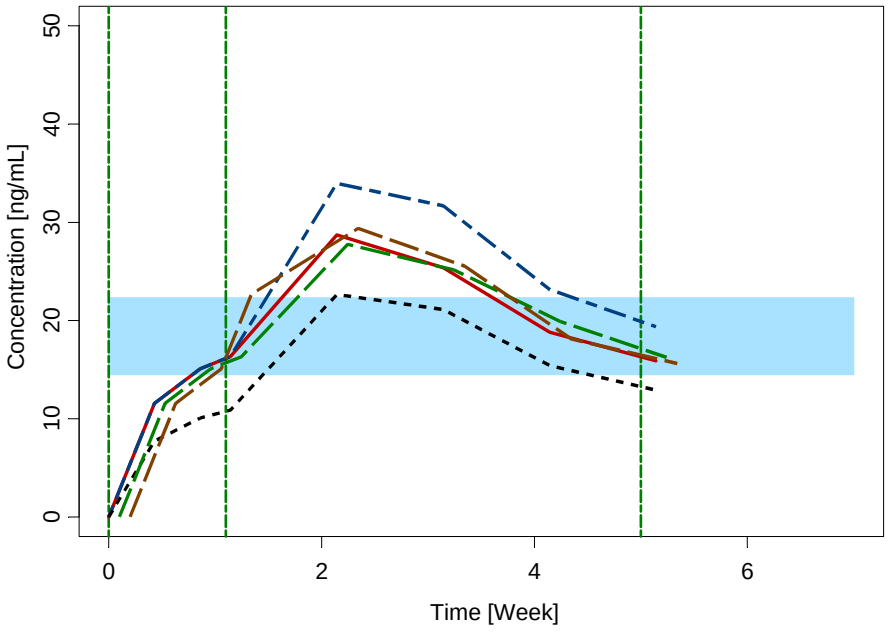
of paliperdione concentration from the prior treatment (such as paliperidone ER and IR formulations) can be neglected by the time when the second initial dosing window is reached. Simulation results demonstrated that paliperidone exposure levels are similar if the second initial dose is given within 2 days prior to or after the scheduled time (Figure 3 A). It is beyond the scope of our simulation to evaluate a patient who is receiving another long acting antipsychic injection before switching to paliperidone palmitate injection.

The second simulation was conducted to evaluate the proposed dosing window for the maintenance dose. As shown in Figure 3 B, the paliperidone concentrations are within the desired concentration range even when paliperidone is administered 1 week prior to or after the scheduled time.

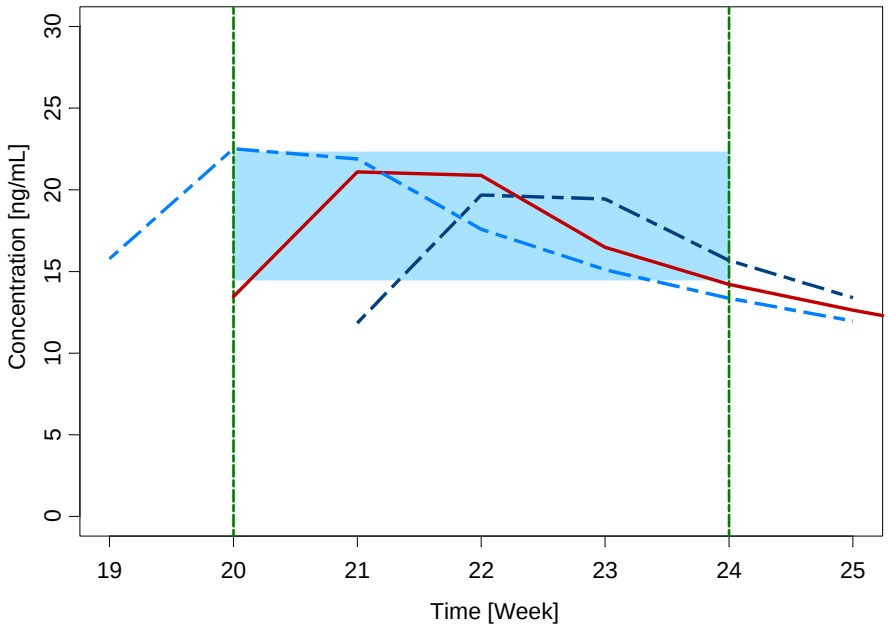
Table 3 the Sponsor Proposed Dosing Window

Dosing	Scheduled Dosing Time	Dosing window
Second Initial Dose	End of the first week	± 2 days
Maintenance Dose	Every 4 weeks	± 7 days

Figure 3 Evaluation of Dosing Window



(A)



(B)

Note:

A) Dashed blue line = 150 mg on Day1 and Day 8

Dashed brown line = 150 mg on Day 1 and 100 mg on Day 6

Solid red line = 150 mg on Day 1 and 100 mg on Day 8

Dashed green line = 150 mg on Day 1 and 100 mg on Day 10

Dashed black line = 75 mg on Day 1 and Day 8

B) Dashed light blue line = maintenance dose 75 mg 1 week prior to the scheduled time

Solid red line = maintenance dose 75 mg on the scheduled time

Dashed dark blue line = maintenance dose 75 mg 1 week after the scheduled time

1.1.3 Is the sponsor proposed re-initiation dosing regimen justified?

The sponsor proposed a re-initiation dosing regimen for patients who miss paliperidone palmitate injection (Table 4). Our simulations indicated that the sponsor's proposal for patients who miss doses for 4-6 weeks and > 6 months are acceptable with the assumption that paliperidone tolerability and the underlying disease progression are not affected due to the missing doses. (b) (4) We recommend that the re-initiation dose for a patient who discontinues paliperidone palmitate treatment for 6 weeks – 6 months be the same as the previous maintenance dose with a maximum of 100 mg.

Table 4 The Proposed and Recommended Re-Initiation Dosing Regimen

	Re-initiation Dosing Regimen	
Missing Time	Dose	Dosing Time
1 month - 6 week	The Same Regular Dose	q 4 week
	(b) (4)	(b) (4)
6 week - 6 month	*: The Same Regular Dose (Up to 100 mg)	Day 1, Day 8, followed by q 4 week
6 month	Restart the initial dosing regimen	

*: FDA reviewer's recommended dose.

If a patient misses paliperidone dose for more than 6 months, the pharmacokinetic profile of paliperidone is shown in Figure 4 A. The results demonstrated that if 6 months have elapsed since the last injection, the concentration is almost zero. Therefore, the patient should restart the initial dose in order to ensure that the desirable concentration range can be reached within 1 week (Figure 4A). If a patient misses a dose for about 1 month to 6 weeks, the pharmacokinetic profile can be found in Figure 4 B. Paliperidone concentration returns to the desirable range rapidly following the administration of paliperidone with regular monthly interval (Figure 4 B).

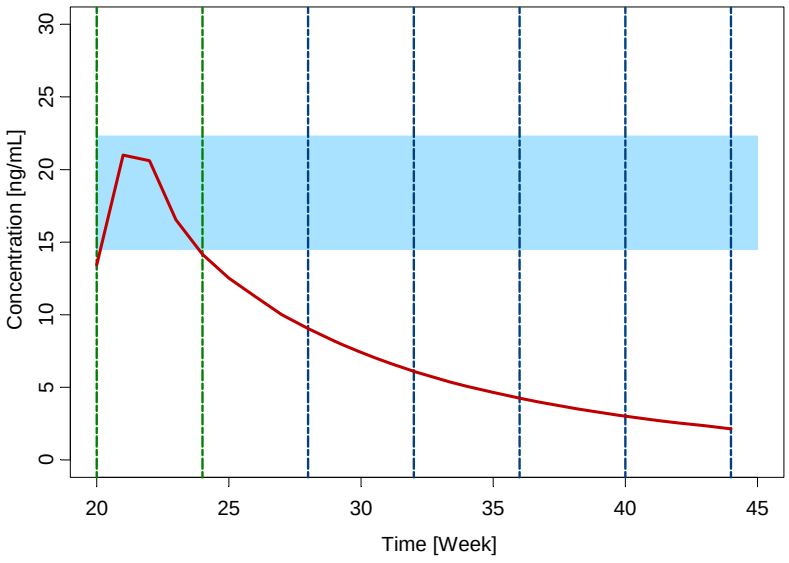
Furthermore, pharmacokinetic simulations were conducted to evaluate the appropriate dosing regimen for a patient who misses doses between 6 weeks to 6 months. The sponsor proposed (b) (4)

The 23% increase in exposure does not lead to safety concern if the patient is stabilized at a dose less than or equal to 100 mg eq, because the overall exposure is still below the highest clinical tested exposure. However, the following example demonstrates how this proposal can lead to potential safety concern. Following the current proposal, (b) (4)

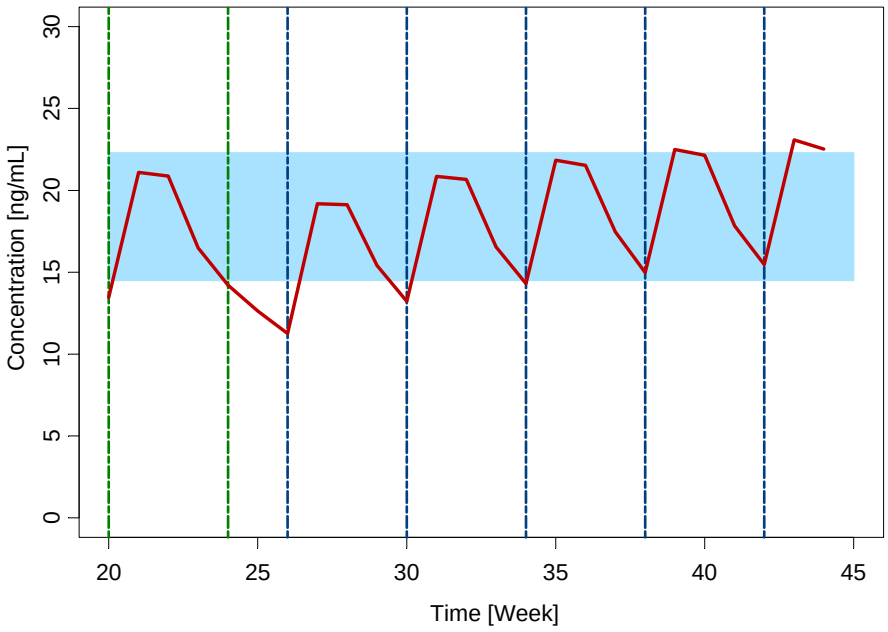
(b) (4)

We recommend the re-initiation dose for a patient who misses dose for 6 weeks – 6 months should not exceed 100 mg. Following our recommendation, the simulated pharmacokinetic profiles were shown in Figure 4E and 4F. Paliperidone concentration will not exceed the highest median exposure observed in the trial. In the mean time, paliperidone exposure returns to the desirable concentration in less than 2-3 dosing cycles.

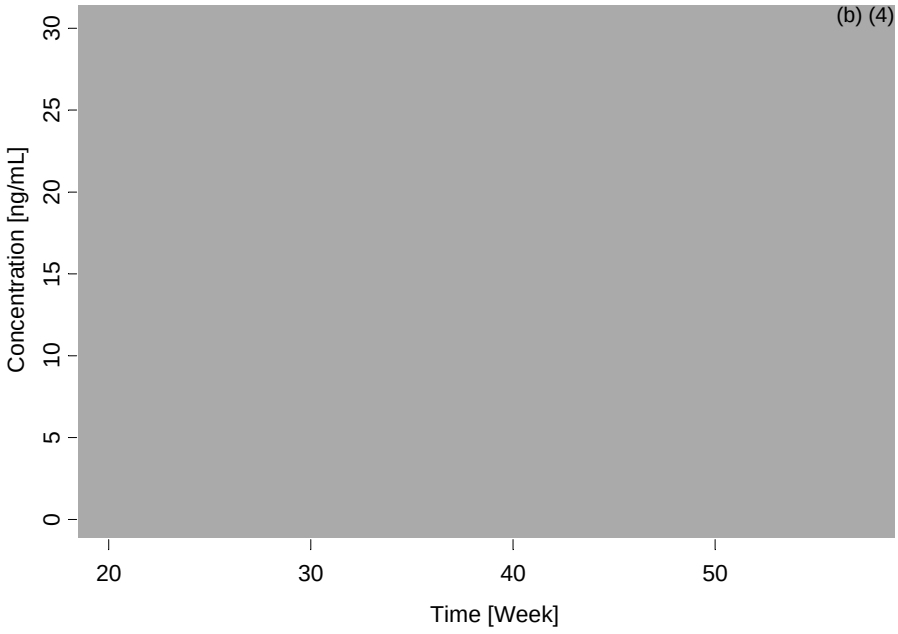
Figure 4 Evaluation of Alternative Dosing Regimen for Missing Dose



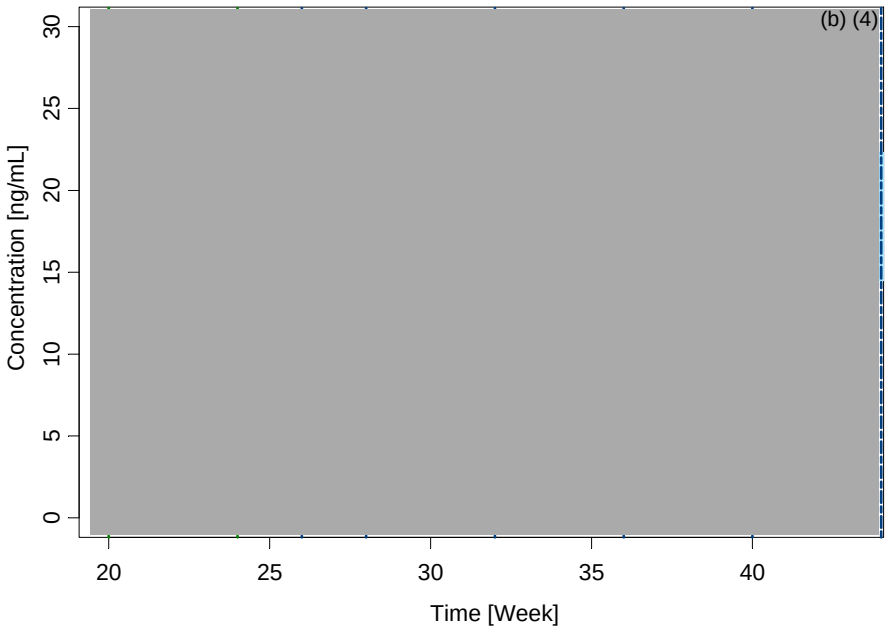
(A)


Concentration [ng/mL]
0
5
10
15
20
25
30
20
25
30
35
40
45
Time [Week]

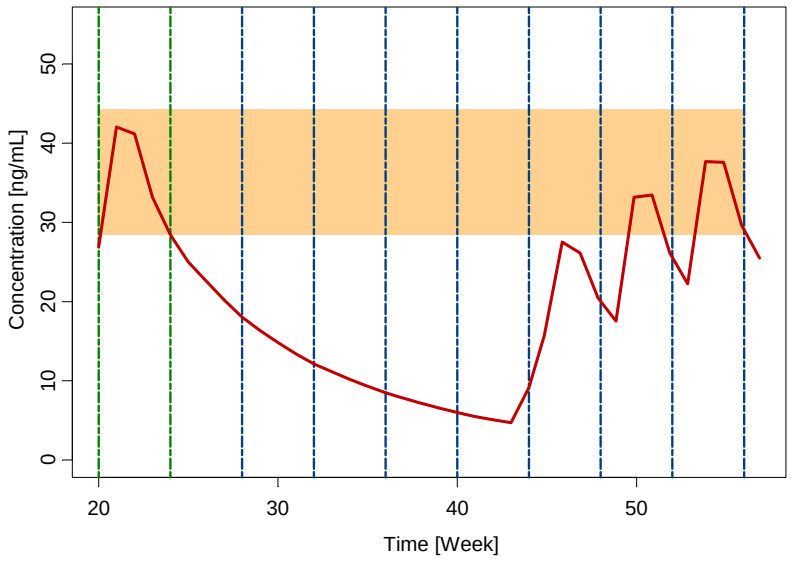
(B)


(b) (4)
Concentration [ng/mL]
0
5
10
15
20
25
30
20
30
40
50
Time [Week]

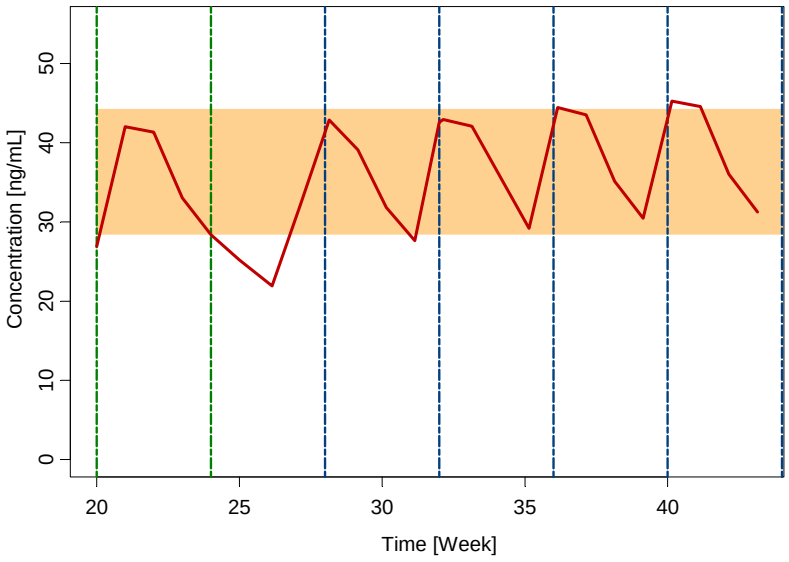
(C)


(b) (4)
Concentration [ng/mL]
0
5
10
15
20
25
30
20
25
30
35
40
Time [Week]

(D)


Concentration [ng/mL]
0
10
20
30
40
50
20
30
40
50
Time [Week]

(E)



(F)

Note:

A = A patient who misses doses for greater than 6 months

B = A patient who misses dose for less than 6 weeks receives the sponsor proposed re-initiation dosing.

C = A patient who misses dose for less than 6 months (6 month minus 1 day) receives the sponsor proposed re-initiation dosing.

D = A patient who misses dose for greater than 6 weeks (6 weeks plus 1 day) receives the sponsor proposed re-initiation dosing.

D = A patient who misses dose for less than 6 months (6 moth minus 1 day) receives the FDA recommended re-initiation dosing.

E = A patient who misses dose for greater then 6 weeks (6 week plus 1 day) receives the FDA recommended re-initiation dosing.

Solid red line = Median PK Profile.

Blue Shaded Area =Median Cmax and Cmin at steady state following 6 mg once daily dosing. (Obtained from Attachment 2.23 in CSR R092670-SCH-01, P-1051)

Brown Shaded Area = Median Cmax and Cmin at steady state following 12 mg once daily dosing.

(Obtained from Attachment 2.23 in CSR R092670-SCH-01, P-1051)

1.1.4 Is the sponsor proposed paliperidone palmitate dosing regimen for patients who intend to [redacted] (b) (4) justified?

No. The sponsor did not provide adequate rationale to support their [redacted] (b) (4) regimen.

The sponsor proposed a paliperidone palmitate dosing regimen for patients who intend to [redacted] (b) (4)

[redacted] (b) (4)

1.1.5 Is the sponsor proposed paliperidone palmitate dosing regimen for patients with mild renal impairment justified?

Yes. The sponsor proposed dosing regimen for patients with mild renal impairment is acceptable.

The sponsor indicated that the initial dosing for patients with mild renal impairment is 100 mg and 75 mg on Day 1 and one week later, respectively. The recommended maintenance dosing is 50 mg q 4 weeks. Paliperidone palmitate is not recommended for patients with moderate and severe renal impairment.

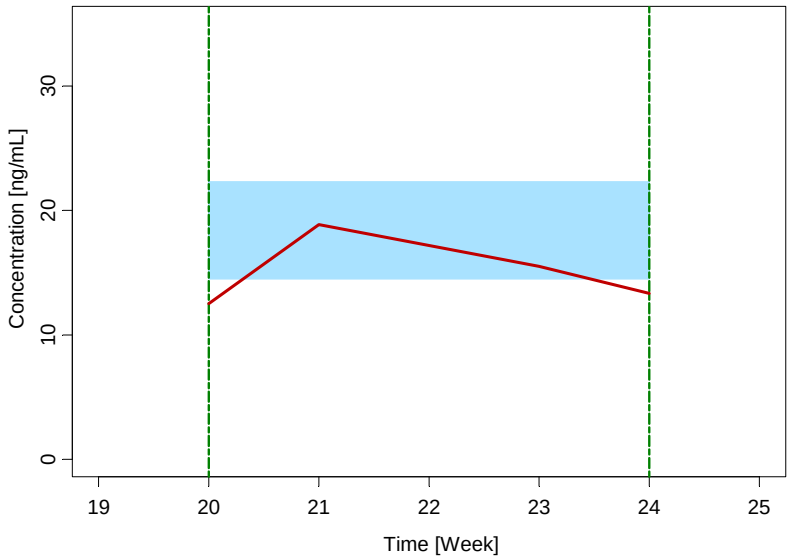
The sponsor's dosing adjustment is necessary for patients with mild renal impairment because paliperidone is mainly excreted through kidney, with 59% of the dose being excreted unchanged into urine. The sponsor's population PK analysis confirmed that creatinine clearance is a significant covariate for paliperidone clearance. Therefore, for a

patient with compromised renal function, paliperidone exposure will be increased if the dose is not adjusted accordingly.

The sponsor proposed maintenance dosing is 50 mg q 4 weeks for patients with mild renal impairment (50 mL/min ≤ creatinine clearance < 80 mL/min). Our simulation was conducted in patients with creatinine clearance of 50 mL/min. Following the sponsor proposed maintenance dosing regimen, paliperidone concentration profile is shown in Figure 5. The steady state concentration is within the desirable concentration range.

The sponsor proposed initial dosing is 100 mg and 75 mg on Day 1 and Day 8. The simulated pharmacokinetic profiles of paliperidone are shown in Figure 6. Even though the peak concentration following the sponsor proposed initial dosing is above the desirable exposure range, the overall exposure is still below the highest clinical tested exposure level (150 mg on both Day 1 and Day 8).

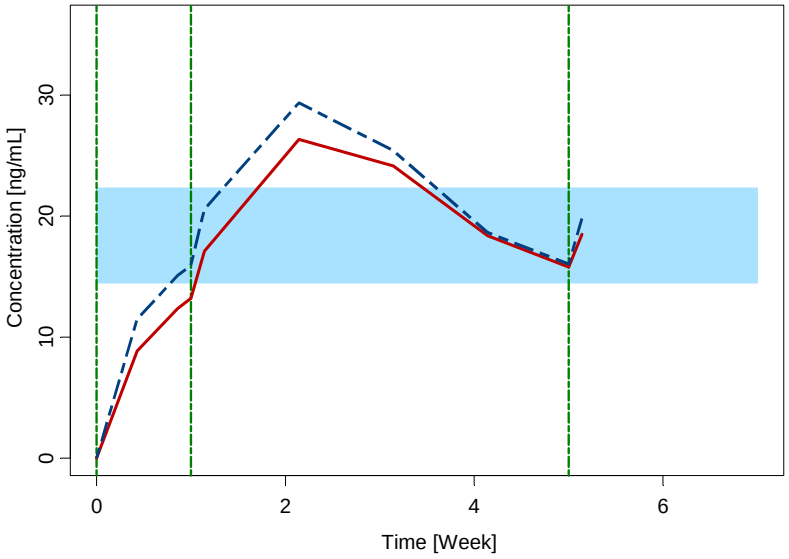
Figure 5 Pharmacokinetic Profile of Palieridone at Steady State Following 50 mg q Paliperidone Palmitate Long Acting Injection q 4 Weeks in Patients with Mild Renal Impairment (CRCL = 50 mL/min)



Note: Solid red line = Median PK Profile.

Shaded Area =Median Cmax and Cmin at steady state following 6 mg once daily dosing was obtained from Attachment 2.23 in CSR R092670-SCH-01, P-1051

Figure 6 Pharmacokinetic Profile of Paliperidone Palmitate Long Acting Injection Following 100 mg / 75 mg on Day1/8



Note: Shaded area = Desirable Concentration range

Solid line = Pharmacokinetic profile for palimperidone in patients with mild renal impairment following the adjusted initial dosing.

Blue dashed line = highest exposure tested in the clinical trial (150 mg on both Day 1 and 1 week later).

1.1.6 (b) (4)

(b) (4)

(b) (4)

Switching from an oral formulation to paliperidone palmitate long acting injection is of less concern because the apparent half-life for an oral formulation is usually short (i.e., < 24 hour). Paliperidone concentration reaches peak within 2 weeks following the initiation dosing (150 mg on Day 1 and 100 mg on Day 8). During the same time, most of the previous antipsychotic drug is eliminated from the body. In the following example, we assume that a patient receiving palieridone ER formulation is intended to switch to the long acting injection. We demonstrated that paliperidone concentration returns to regular therapeutic exposure within one week and the peak concentration is below the highest exposure tested in the trial, following the standard initiation dosing (Figure 1 A). In addition, our simulation indicated that similar steady state paliperidone exposure following various doses of paliperidone ER formulation can be achieved by using palieridone long acting injection (Table 5).

Table 5 Similar paliperidone exposure at steady state using different doses of INVEGA ® and INVEGA ® SUSTNNA ™

Formulation	INVEGA ® Extended Release Tablet	INVEGA ® SUSTENNA ™ Injection
Dosing Frequency	Once Daily	Once every 4 Weeks
Dose (mg)	12	234
	6	117
	3	39-78

One proposal is to use palieridone ER formulation between the two long acting injections. This would allow the physician to titrate paliperidone dose to compensate the elimination of the previous antipsychotic drug based on the clinical response and also provide a flexible regimen to adjust the dose timely for adverse events. After the patient is stabilized on paliperidone ER formulation and most of the previous antipsychotic drug is

eliminated, the paliperidone palmitate injection can be started with the standard initiation dosing.

For patients that cannot follow the proposed switching strategy, the alternative proposal is to switch the patients to the maintenance dosing of paliperidone palmitate long acting injection without the loading dose. However, the appropriate maintenance dose will be determined by the physician's clinical judgment and cannot be established by using pharmacokinetic simulation alone.

1.1 Recommendations

The sponsor proposed initial and maintenance dosing regimen, alternative dosing window, and dosing regimen for patients with mild renal impairment are acceptable from clinical pharmacology point of view.

However, we found:

- (b) (4) .
- (b) (4)

We recommend that the re-initiation dose for a patient who misses paliperidone long acting injection for 6 weeks to 6 months should not exceed 100 mg.

1.1 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing[2]

(b) (4)

(b) (4)

3 pp withheld in full immediately after this page as (b)(4) Draft Labeling

2 PERTINENT REGULATORY BACKGROUND

Paliperdione has been marked as an extended release (ER) formulation with a once-daily administration schedule for the treatment of schizophrenia. Paliperidone palmitate (b) (4) was originally submitted by Johnson & Johnson Pharmacetucial Research and Development (J&JPRD) on 25 October 2007. On 25 August 2008, the division issued a complete response letter. Following the complete response letter, meetings for the discussion of the resubmission were held on 9 September 2008 and 21 November 2008. J&JPRD filed a resubmission on 03 February 2009 to address the comments raised by the division in the complete response letter.

In the resubmission package, the sponsor included a recently completed R092670-PSY-3007 clinical study report to support the initial and maintenance dose of (b) (4). An interim analysis of safety data from Study R092670-PSY-1008, a long-term (up to 53 weeks), open-label, safety study, was also provided to support the use of a higher initiation and maintenance dose.

3 RESULTS OF SPONSOR'S ANALYSIS

1.1 Summary of the Clinical Study Report: (R09267-PSY-3007)

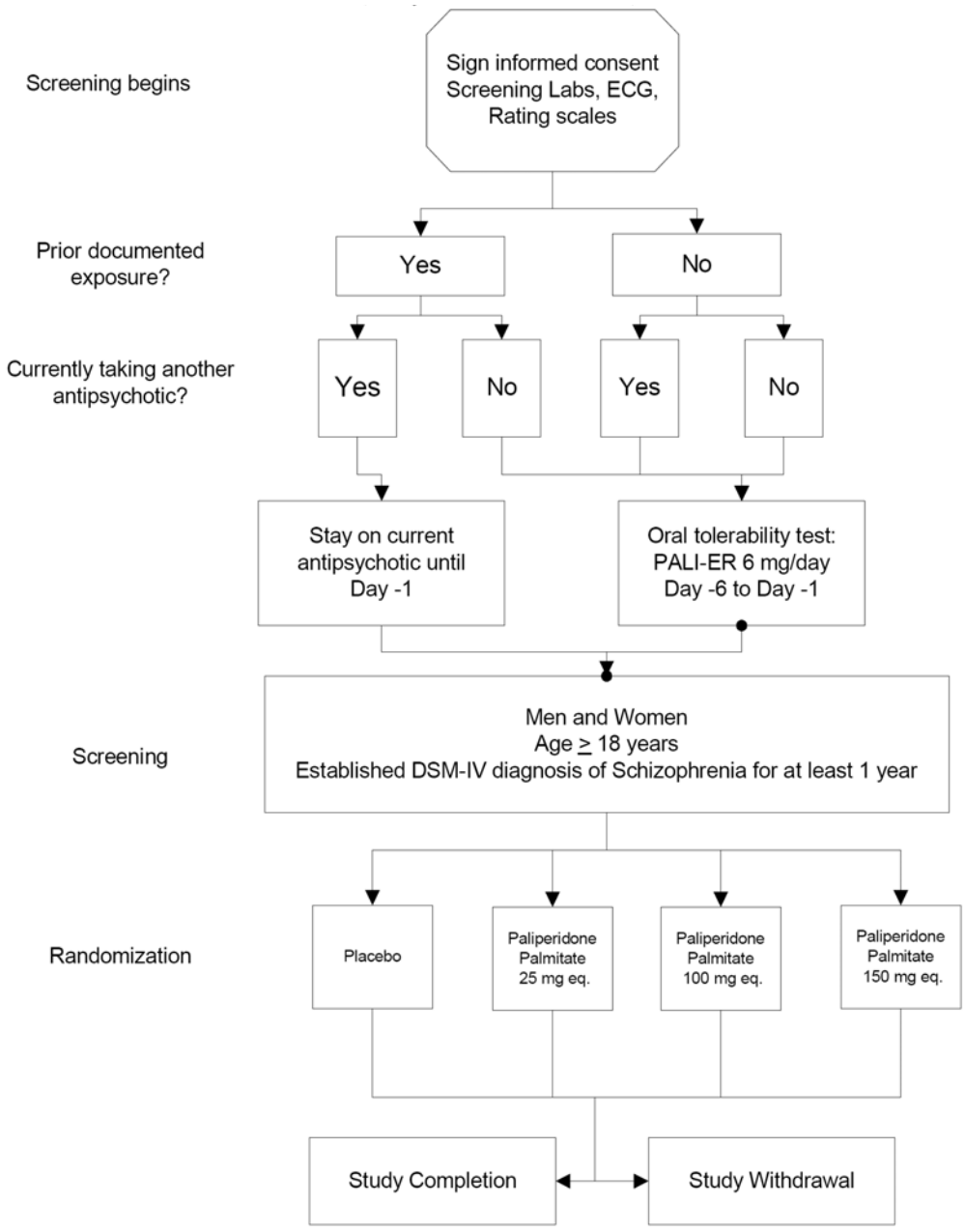
Study R092670-PSY-3007 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-response study designed to evaluate the efficacy and safety of 3 fixed maintenance doses of paliperidone palmitate (25, 100, and 150 mg eq.) compared with placebo. Study medication was administered as 4 doses: an initial i.m. injection of placebo or paliperidone palmitate 150 mg eq. followed by 3 fixed i.m. doses of placebo or paliperidone palmitate (25, 100, or 150 mg eq.) on Days 8, 36, and 64. The initial dose of study medication was given in the deltoid muscle. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator. Randomized subjects were to remain in the study for 28 days after the last injection on Day 64 with the end of study visit scheduled for Day 92 during the double-blind period. The study included a screening period of up to 7 days and a 13-week double-blind treatment period (Figure 7). The screening period included a washout of disallowed psychotropic medications. The entire study, including the screening period, lasted approximately 14 weeks. The screening period included oral tolerability testing for subjects without documented previous exposure to risperidone or paliperidone. Subjects

with documented previous exposure to the above medications and currently taking another antipsychotic regimen continued their current treatment through Day –1. If required, tolerability testing could overlap with the washout period. It was planned that approximately 644 subjects (161 in each of 4 treatment groups) aged 18 years or older, with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association 1994) diagnosis of schizophrenia for at least one year before screening and severely symptomatic (Positive and Negative Syndrome Scale (PANSS) total score between 70 and 120, inclusive, at screening) would participate in the double-blind period of this study. Randomized subjects were to remain in the trial for 28 days after the last injection on Day 64 with the end of the study visit scheduled for Day 92 during the double-blind period. PK samples were collected on Day 1, prior to the first injection and on Days 2, 4, 6, 8, 15, 22, 64, and 92. Efficacy and safety were evaluated regularly throughout the study.

PK samples were evaluated by using non-linear mixed effects modeling. The primary endpoint for efficacy was the change in PANSS total score from baseline (i.e. the start of double-blind treatment, Day 1) to the end of the double-blind treatment period (i.e., Day 92 or the last post baseline assessment). Safety was monitored by the evaluation of adverse events, extrapyramidal symptom (EPS) rating scales (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Rating Scale [BARS], Simpson and Angus Rating Scale [SAS]) scores, clinical laboratory test results, vital signs measurements, electrocardiograms (ECGs), and physical examination findings. In addition, the tolerability of injections was assessed; the investigators evaluated injection sites and the subjects assessed injection pain.

Figure 7 Study Design

(Study R092670-PSY-3007)



Note: The study medication was administered as 4 doses: an initial i.m. injection of placebo or paliperidone palmitate 150 mg eq. followed by 3 fixed i m. doses of placebo or paliperidone palmitate (25, 100, or 150 mg eq.) on Days 8, 36, and 64. The initial dose of study medication was given in the deltoid muscle. Subsequent injections were given either in the deltoid or gluteal muscle at the discretion of the investigator.

All randomized subjects who received at least 1 dose of double-blind study drug and had both baseline and at least one post baseline efficacy measurement during the double-blind treatment period were included in the intent-to-treat efficacy analyses. The change from baseline in PANSS total score at each visit and at end point was analyzed using an ANCOVA model. LOCF method was used to account for subjects who prematurely discontinued the trial. Dunnett's test was used to adjust for multiple comparisons for the

3 paliperidone palmitate dosage versus placebo. The primary efficacy analysis results were shown in Table 6.

Table 6 PANSS Total Score Change from Baseline to End Point LOCF with Dunett-Bonferroni-Based Parallel Gatekeeping Procedure

(ITT Analysis Dataset)

	Placebo (N=160)	R092670 25 mg eq. (N=155)	R092670 100 mg eq. (N=161)	R092670 150 mg eq. (N=160)
Baseline Mean (SD)	86.8 (10.31)	86.9 (11.99)	86.2 (10.77)	88.4 (11.70)
End point Mean (SD)	83.9 (21.44)	78.8 (19.88)	74.6 (18.06)	75.2 (18.59)
Change from Baseline				
Mean (SD)	-2.9 (19.26)	-8.0 (19.90)	-11.6 (17.63)	-13.2 (18.48)
P-value (minus Placebo)[a]		0.034	<0.001	<0.001
Diff. of LS Means (SE)		-5.1 (2.01)	-8.7 (2.00)	-9.8 (2.00)

[a] Based on analysis of covariance (ANCOVA) model with treatment (Placebo, R092670 25 mg eq., R092670 100 mg eq., R092670 150 mg eq.) and country as factors, and baseline value as a covariate. P-values were adjusted for multiplicity for comparison with placebo using Dunnett's test.

Note: Negative change in score indicates improvement.

Paliperidone palmitate, injected at a dose of 150 mg eq. into the deltoid muscle followed by 3 i.m. injection at fixed dose of 25 mg eq., 100 mg eq., or 15o mg eq. on Days 8, 36, and 64, was generally well tolerated by adult subjects with schizophrenia during the study (Table 7).

Table 7 Overall Summary of Treatment-Emergent Adverse Events

(Safety Analysis Dataset)

	Placebo (N=164) n (%)	R092670 25 mg eq. (N=160) n (%)	R092670 100 mg eq. (N=165) n (%)	R092670 150 mg eq. (N=163) n (%)	Total (N=652) n (%)
TEAE	107 (65.2)	101 (63.1)	99 (60.0)	103 (63.2)	410 (62.9)
Possibly related TEAE[a]	47 (28.7)	45 (28.1)	49 (29.7)	51 (31.3)	192 (29.4)
TEAE leading to death	0	0	0	1 (0.6)	1 (0.2)
1 or more serious TEAE	23 (14.0)	15 (9.4)	22 (13.3)	13 (8.0)	73 (11.2)
TEAE leading to permanent stop	11 (6.7)	10 (6.3)	10 (6.1)	13 (8.0)	44 (6.7)

[a] Study drug relationships of possible, probable, and very likely are included in this category.

Adverse events are coded using MedDRA version 10.1

1.1 Summary of the Population PK Study Report: (Population Pharmcokinetics of Paliperidone Palmitate: Model Update with R092670PSY3007 Data)

The sponsor evaluated the previous submitted population PK model (reviewed by Dr. John Duan for the original submission of NDA 22264) for paliperidoen palmitate with the new data from Study R092670PSY3007. The design of Study R092670PSY3007 and PK sampling schedule were summarized in Section 3.1. The PK model was shown in Figure 8. This is a one-compartment model with first order elimination. The absorption component of the model allowed a fraction of the dose to enter relatively quickly into the

central compartment via a zero order process. After some lag-time the remaining fraction then entered the systemic circulation via a first order process.

The sponsor took different steps in order to evaluate the model. A visual predictive check was performed. The model prediction appeared to be in good agreement with the PK observations from Study R092670PSY3007 (

Figure 9). Subsequently, PK observations from Study R092670PSY3007 were used for external validation. The model prediction was quantitatively compared with the observations (Table 8). The PE% and |PE|% between the PK observation and model prediction were 1.57% and 14.5% respectively. Furthermore, the model results were directly compared using historical dataset (without Study R092670PSY3007) versus using the updated dataset (with Study R092670PSY3007). The goodness of fit plots for the execution of the final model on the combined data indicated that current model adequately described PK observations from the new study (Figure 10). All PK parameters either remained the same or changed very minimally when new data were included (

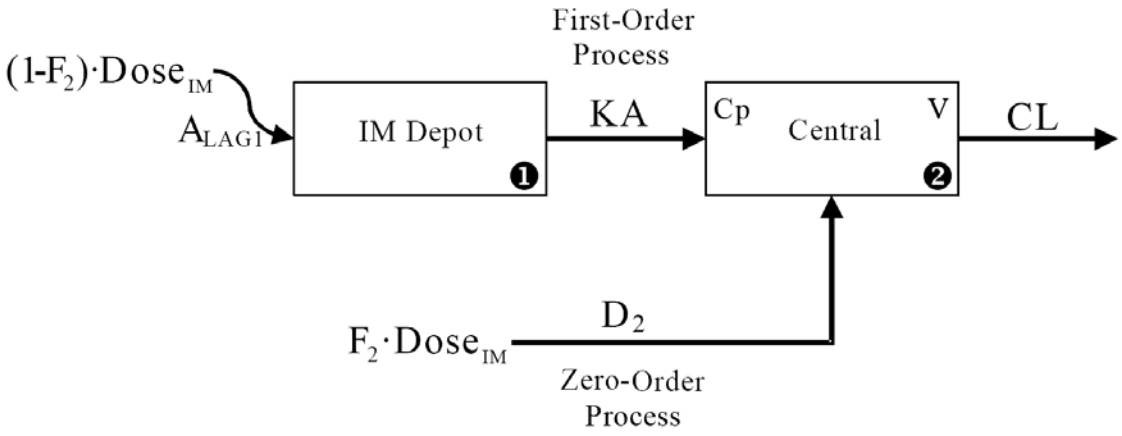
Table 9).

The main outcomes of this analysis are as follows: (i) Initiation with a paliperidone palmitate dose of 150 mg eq. in the deltoid muscle and the appropriate needle length led to rapid achievement of target concentrations and this regimen may serve as a suitable initiation regimen for this long acting injectable formulation; and (ii) R092670PSY3007 data are in excellent agreement with prior knowledge about paliperidone palmitate population-pharmacokinetics. This was confirmed by the observation that all PK parameters either remained unchanged or changed very minimally when the new data were added to the previous dataset.

Review's comments:

1. *The sponsor's population PK model appears to adequately describe the PK observations from Study R092670PSY3007.*

Figure 8 Schematic Presentation of the Population Pharmacokinetic Model



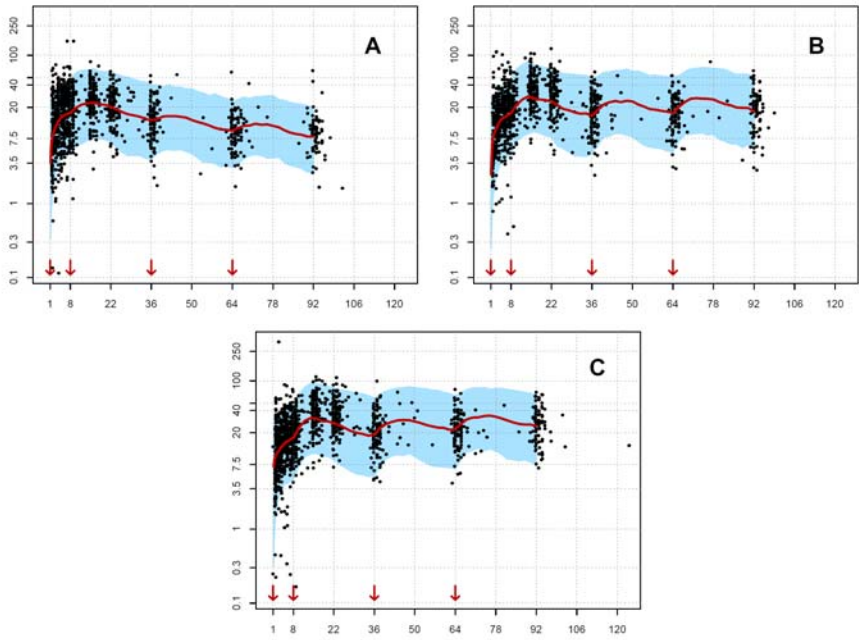
Note: Alag = Lag time for the first order absorption process; CL =clearance; Cp=plasma concentration; D2=duration of zero order input; F2=faction of dose entering via zero order input; IM=intramuscular; KA=first order absorption rate constant; V=volume of distribution

Table 8 Tabular Results for External Validation: Distribution of PE% and |PE|%

	N	Observed Median	Median cut-off to pass validation	Observed 25th percentile	Observed 75th percentile
Prediction error percents (PE%)	3633	1.57	±15	-13.0	15.7
Absolute prediction error percents (|PE|%)	3633	14.5	30	6.63	25.7

Note: $PE\% = (DV_{ij} - PRED_{ij})/PRED_{ij} * 100$; $|PE|\% = |PE\%|$

Figure 9 Comparison of Population PK Simulation vs. Acutal Plasma Concentration Data from Study R092670PSY3007



The x-axis represents time (days) and the y-axis represents plasma concentrations of paliperidone (ng/mL). The arrows represent days of injection with paliperidone palmitate. The solid line and the shaded area represent the median and the 90% prediction interval based on the population PK simulation. Filled circles represent actual plasma concentration data from clinical trial subjects (paliperidone palmitate 150 mg eq. on Day 1 deltoid, followed by paliperidone palmitate [A] 25 mg eq. [B] 100 mg eq. [C] 150 mg eq. dose in either the deltoid or the gluteal muscle on Days 8, 36 and 64.

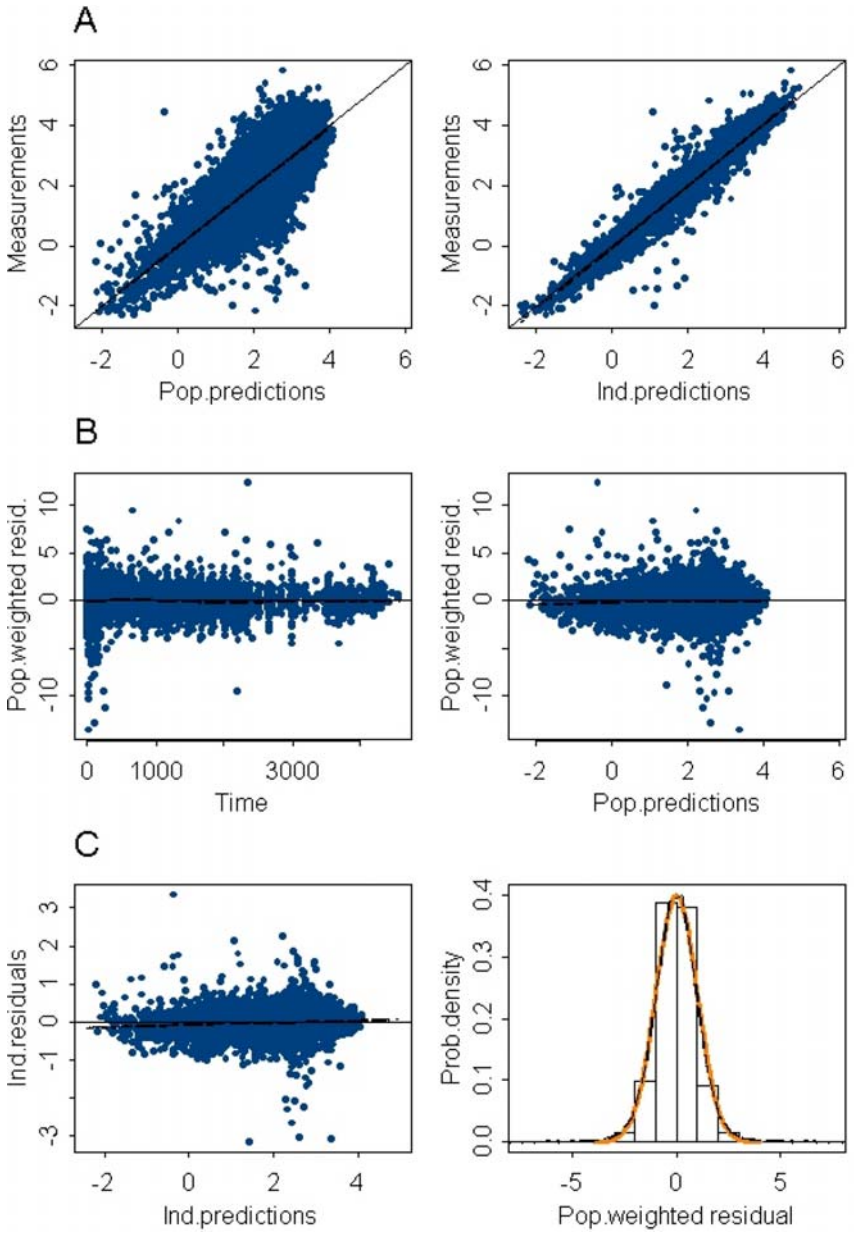
Table 9 Final Model Parameters with and without R092670PSY3007 Data*

	Index set + R092670PSY3007		Index Dataset	
Parameter	Estimate	Precision (CV%)	Estimate	Precision (CV%)
CL (L/hr)	4.98	3%	4.87	2%
CL - CRCL Power	0.377	21%	0.387	15%
V: Shift factor for Females	0.844	9%	0.749	11%
V (L)	336	6%	368	6%
V - BMI Power	0.64	74%	0.968	3%
KA: Shift factor for Females	0.799	5%	0.784	6%
KA: Shift factor for Deltoid Injection	1.23	3%	1.2	4%
KA x 10^3 (hr^{-1})	0.53	8%	0.51	5%
KA: Age Power	0.346	16%	0.318	28%
KA: Injection Volume Exponent	0.292	40%	0.36	12%
ALAG1 or D2 (hr)	376	1%	373	1%
F2: Shift factor for Females	0.864	4%	0.8	4%
F2: Shift factor for Deltoid Injection	1.38	3%	1.32	4%
F2: Shift factor Deltoid 1.5 inch needle	1.31	5%	1.5	6%
F2	0.199	5%	0.192	5%
F2: BMI Power	0.656	29%	0.558	23%
F2: Injection Volume Exponent	0.218	34%	0.264	15%
IIV CL (CV%)	42%	7%	42%	9%
IIV V (CV%)	74%	28%	71%	15%
IIV KA (CV%)	52%	19%	58%	11%
IIV F2 (SD) †	0.057	27%	0.061	21%
IOV CL (CV%)	24%	11%	27%	15%
IOV V (CV%)	21%	62%	21%	41%
IOV F2 (SD) †	0.081	16%	0.079	12%
RV Sigma (SD)	0.25	7%	0.24	8%

† IOV and IIV for F2 is computed for 100 mg eq. gluteal injection for a male subject with BMI of 27 kg/m^2

*: Parameters were derived using subjects without oral tolerability test.

Figure 10 Goodness of Fit Plots for Pooled Data with Information from Study R092670PSY3007



1.1 Summary of the Population PK Simulation Results

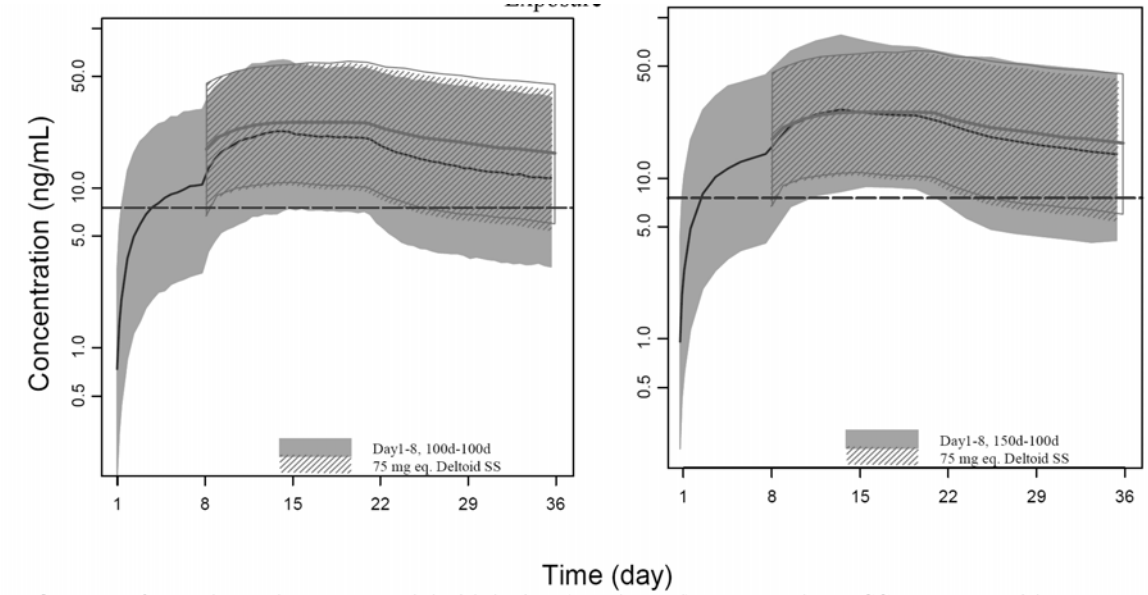
The sponsor submitted their population PK simulation results in the clinical overview. The objectives of the simulations were to assess the following aspects of the dosing strategy for paliperidone palmitate:

- Initiation regimen
- Maintenance regimen
- Overall recommended regimen
- Flexibility in the dosing window for initiation and maintenance therapy

- Re-initiation regimen
- Switching from other antipsychotics

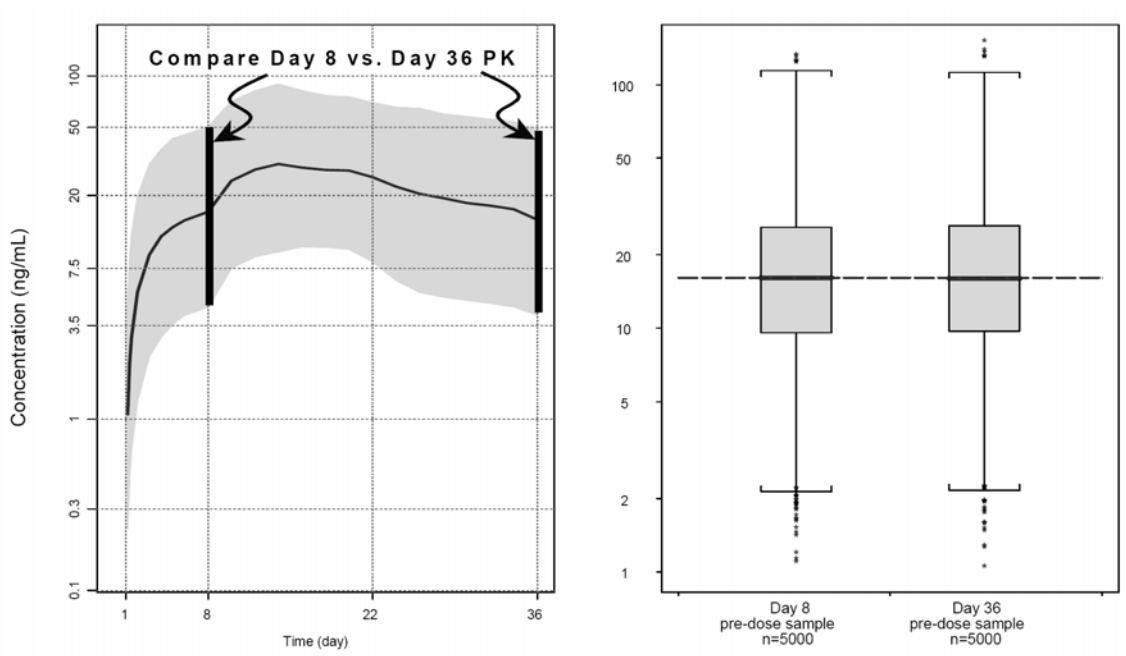
The sponsor's simulations supported using 150 mg and 100 mg dose on Day 1 and Day 8 as the initial dose. The first dose of 150 mg eq leads to 84% of the subjects reaching the threshold concentration of 7.5 ng/mL. A second dose of 100 mg eq yields a quick achievement of the steady state concentration with 75 mg eq as the maintenance dose (Figure 11). Based on the results from Study R092670-PSY-3007, the initial dosing is safe and effective. In addition, the PK exposures are similar on Day 8 and Day 36 following the initial dosing. The model prediction is in agreement with the clinical observations (Figure 13).

Figure 11 Week 2 to 5 Exposure vs. Steady State Exposure



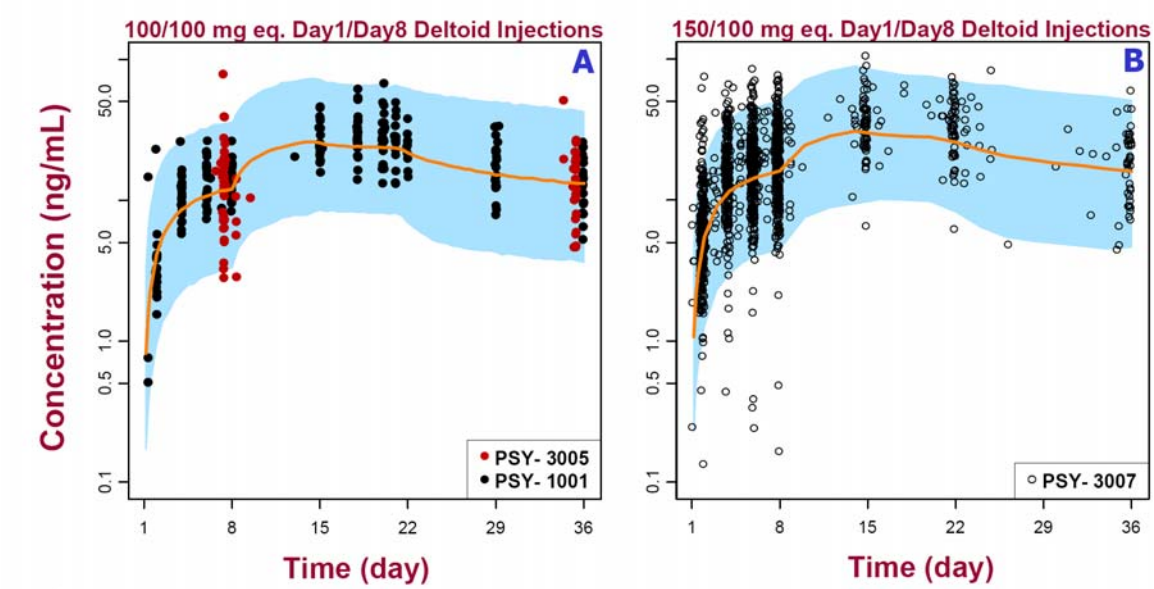
NOTE: [Left panel] 100/100 mg eq. deltoid dosing (100d-100d) on Day 1/8 vs. SS exposure with 75 mg eq. deltoid dosing; [Right panel] 150/100 mg eq. deltoid dosing (150d-100d) on Day 1/8 vs. SS exposure with 75 mg eq. deltoid dosing. Lines and shaded areas represent the median and 90% prediction interval.

Figure 12 Day 8 and Day 36 Pre-Dose Exposure After 150/100 mg eq Dosing on Day 1/8



NOTE: [Left panel] Temporal profile with this dosing regimen; lines and shaded areas represent the median and 90% prediction interval; [Right panel] Histograms of Day 8 vs. Day 36 pre-dose exposure

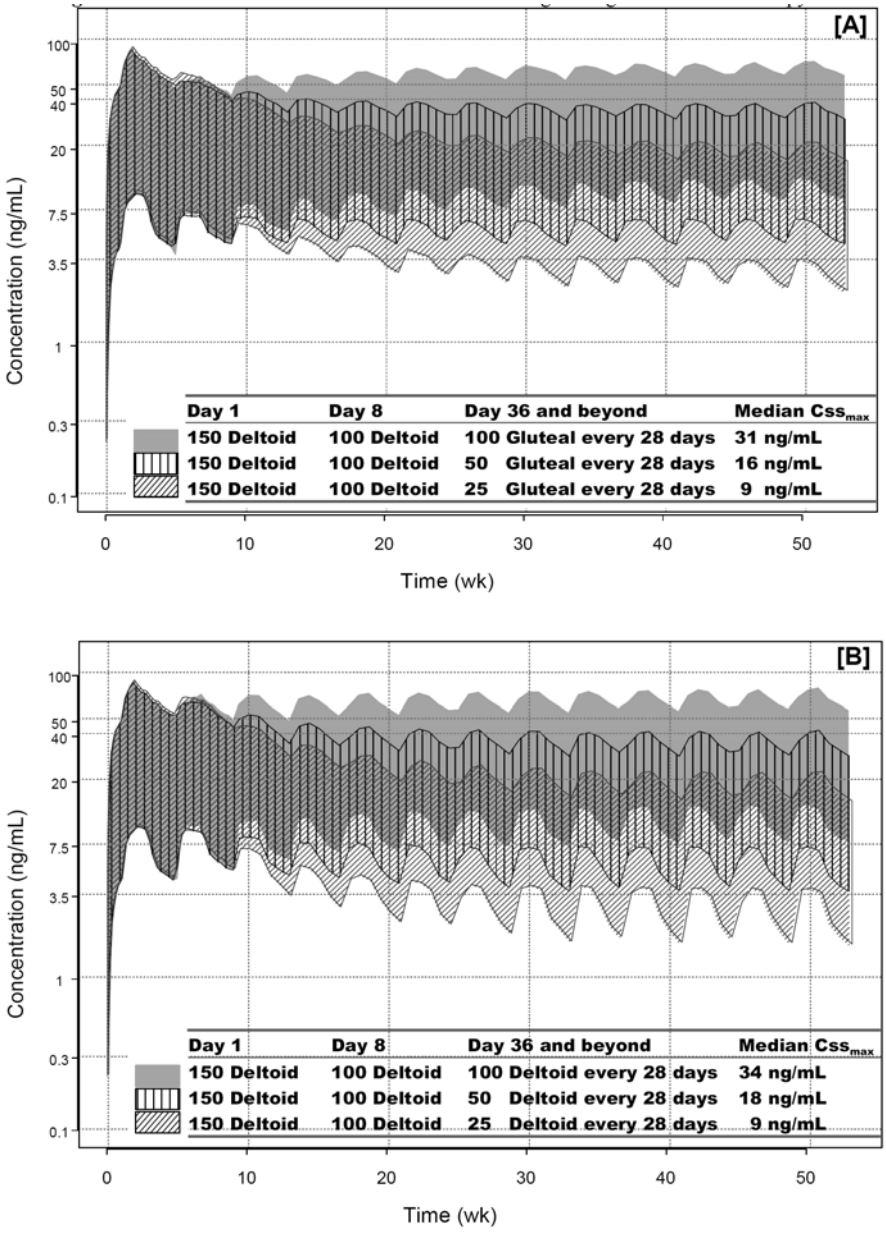
Figure 13 Comparison of Model-based Prediction vs. Observed Data for the Initial 5-Weeks of Treatment With Different Initial Doses



NOTE: [A] 100/100 mg eq. deltoid dosing on Days 1 and 8; [B] 150/100 mg eq. deltoid dosing on Days 1 and 8. The lines and the shaded areas represent the model based medians and 90% prediction intervals. PSY-3005 data in Figure 34A are jittered along the X-axis to avoid overlap of concentrations around Day 8 and Day 36.

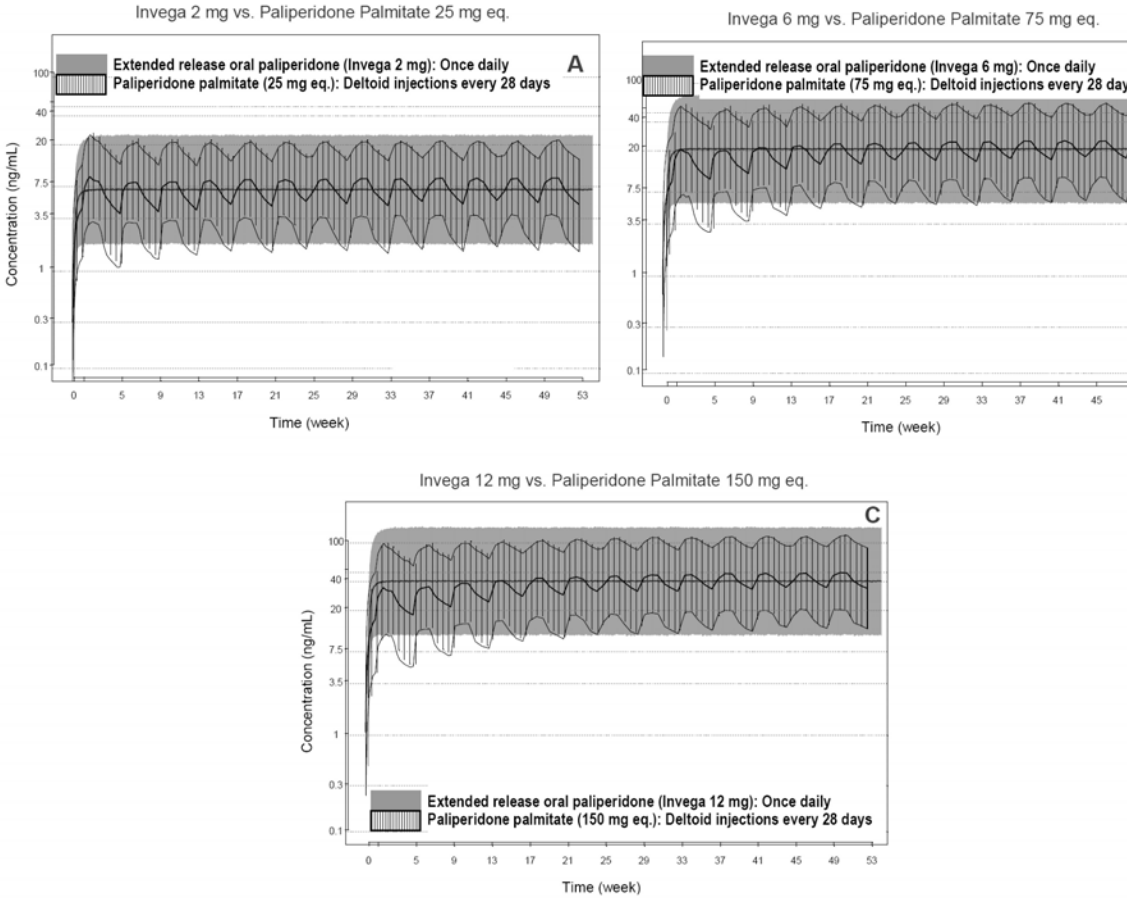
The sponsor then evaluated the maintenance dosing. Figure 14 Showed similar exposure levels following different muscle injections. A similar exposure can be found between 150, 75, 25 mg eq injection versus 2, 6, 12 mg eq ER formulation (Figure 15). The PK following the conversion from 6 mg qd paliperidone ER formulation to 75 mg q 4 week long-acting injection can be seen in Figure 16.

Figure 14 Simulation for Deltoid vs. Gluteal Muscle Injection During Maintenance Dosing



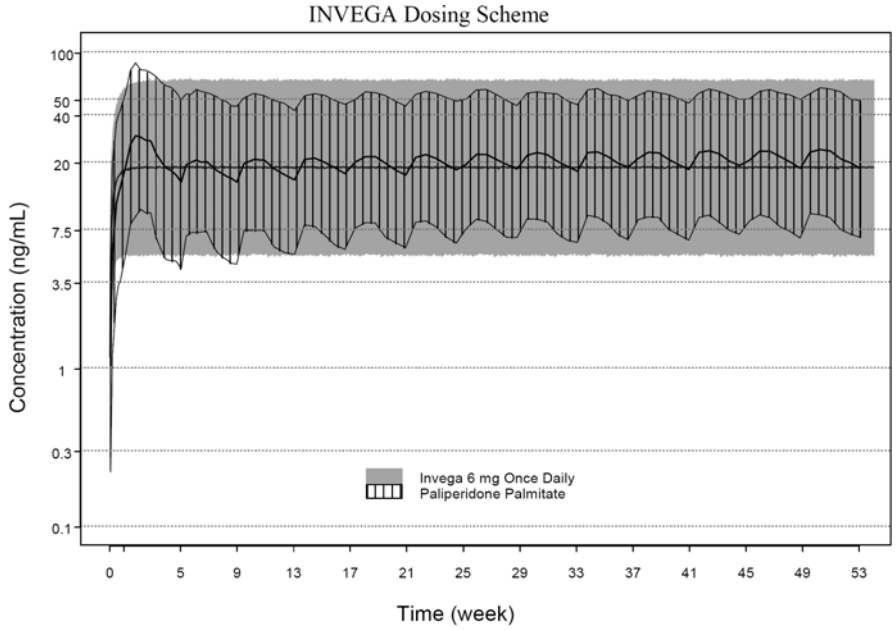
[A] 150/100 mg eq. deltoid dosing on Days 1 and 8 scenario where the injection site is switched from the deltoid to the gluteus muscle after the second injection; [B] 150/100 mg eq. deltoid dosing on Days 1 and 8 scenario where the deltoid site is also used for maintenance therapy. The shaded/hatched regions represent the 90% prediction interval.

Figure 15 Simulation Comparison of Paliperidone ER vs. Paliperidone Palmitate



NOTE: [A] low; [B] medium; and [C] high doses. The lines and the shaded areas represent the model based medians and 90% prediction intervals.

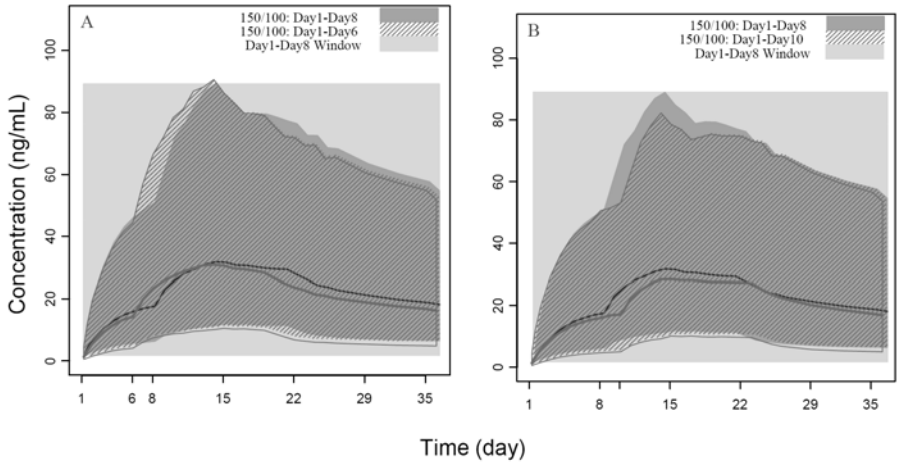
Figure 16 Current Recommended Paliperidone Long Acting Injection vs. Recommended INVEGA Dosing Schedule



NOTE: The recommended regimen for paliperidone palmitate is 150/100 mg eq. on Day 1/Day 8 followed by 75 mg eq. maintenance dosing. Similarly, the recommended regimen for INVEGA is a daily 6 mg dose. The lines and the shaded areas represent the model based medians and 90% prediction intervals.

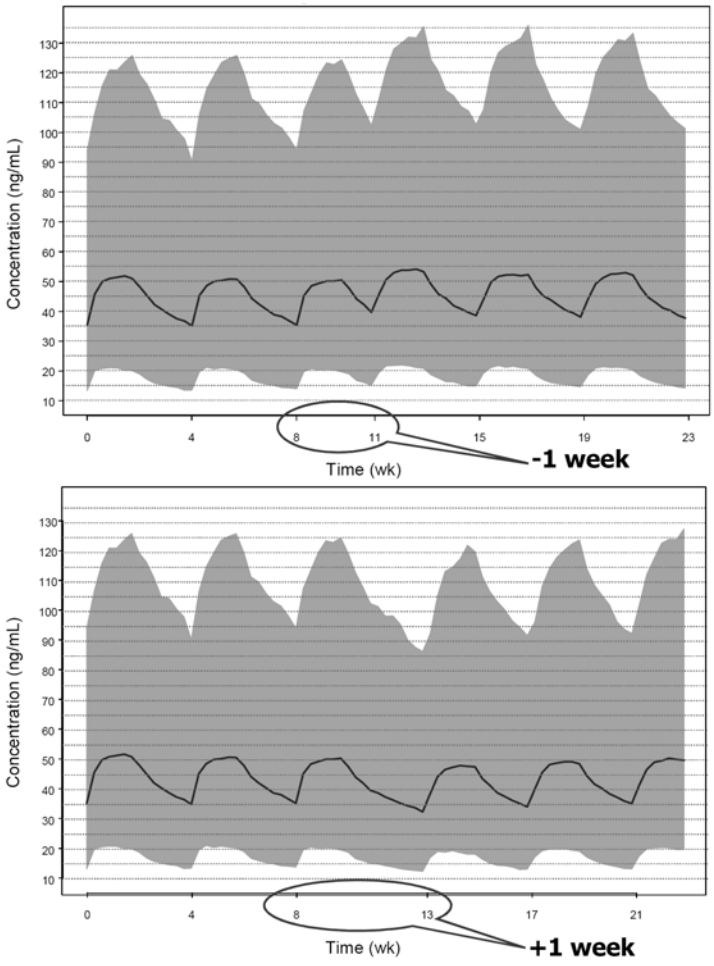
The sponsor compared the PK levels for flexibility on Day 8 and monthly dosing window (Figure 17 and Figure 18) and showed similar exposure levels.

Figure 17 Simulation for Flexibility in the Day 8 Window



[A] 150/100 mg eq. Day 1/Day 8 initiation vs. 150/100 mg eq. day1/day6 initiation; and [B] 150/100 mg eq. Day 1/Day 8 initiation vs. 150/100 mg eq. Day 1/Day 10 initiation. Lines and shaded areas (pink and grey hatched regions) represent medians and 90% prediction intervals. Blue shaded area represents the exposure window for the Day 1/Day 8 regimen.

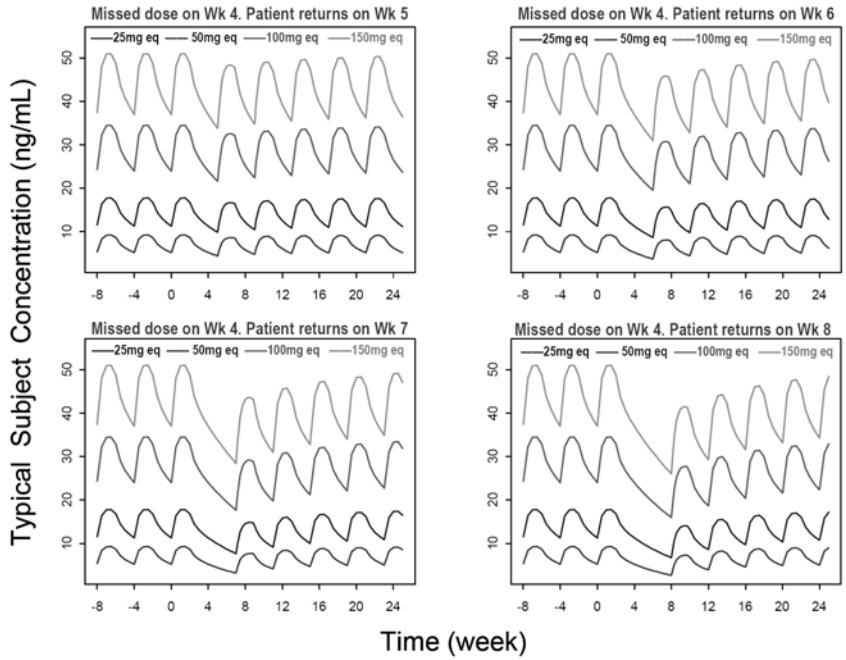
Figure 18 Flexibility in Dosing Window Around Normally Scheduled Monthly Injection



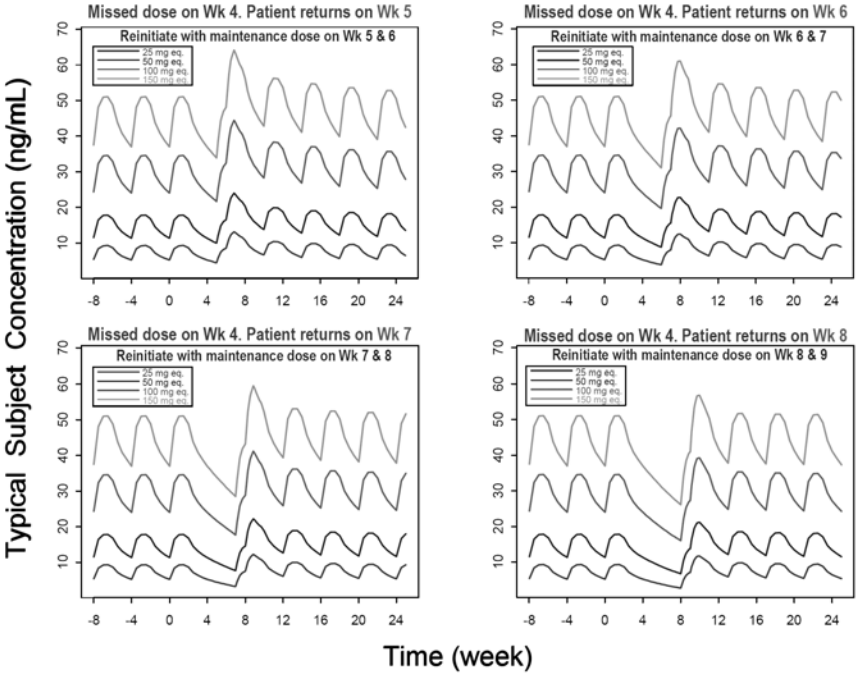
NOTE: Lines and shaded areas represent medians and 90% prediction intervals.

Re-initiation of treatment regimen after a missed injection at steady state was evaluated. Figure 19 demonstrated the PK profile after missed dose and re-initiation of the treatment within 6 months. After 6 months, the PK profile decreases almost to zero. Initial dose is required to achieve the optimal exposure (Figure 20).

Figure 19 Deterministic Simulations for Re-initiation Regimen Under The Various Missed Dose Scenarios

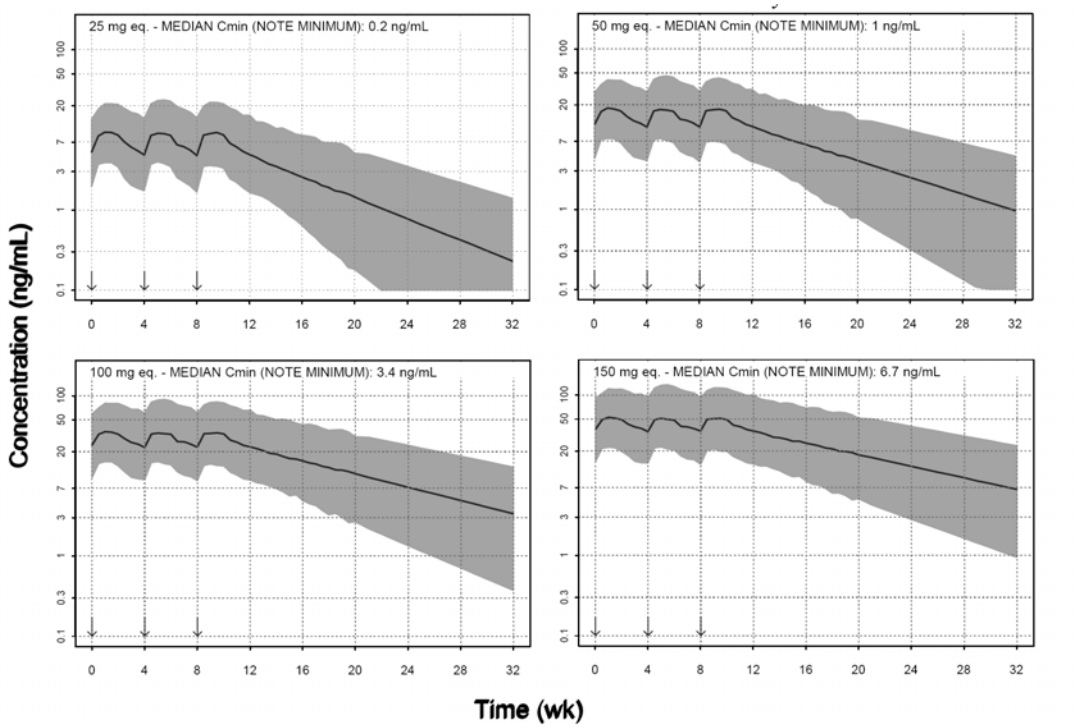


NOTE: Reinitiation occurs with a single maintenance dose at the time point when the patient returns followed by regular monthly dosing.



NOTE: Reinitiation occurs with 2 maintenance doses separated by one week at the time point when the patient returns followed by regular monthly dosing.

Figure 20 Plasma Concentration Profiles for the Entire Dosing Range of 25-150 mg eq. When Therapy is Discontinued For 6 Months After Achievement of PK Steady State



Lines and shaded areas represent medians and 90% prediction intervals.

The sponsor proposed (b) (4) The PK profile from the sponsor's simulation is shown in Figure 21.

Lines and shaded areas (violet region) represent medians and 90% prediction intervals.

Reviews Comments:

1. *We conducted our independent simulation to verify the sponsor's results. (See reviewer's analysis section)*

2. (b) (4)

4 REVIEWER'S ANALYSIS

The reviewer's analysis was conducted to evaluate the dosing regimen for paliperidone palmitate long-acting injection.

1.1 Introduction

In the original submission, the sponsor proposed an initial dose of (b) (4) eq given on Day 1 and by the end of the first week. In the current submission, the sponsor proposed a different initial dose (i.e. 150 mg eq) based on Study R092670-PSY-3007 (

Table 10). Clinical tested dosing regimens were listed in Table 11. In addition, the sponsor proposed a target maintenance dose of 75 mg eq in the current submission.

(b) (4)

Table 11 Initial and Maintenance Doses being Investigated in the Clinical Trials

Dose Evaluated				Clinical Trial	Document	Date
Initial (mg eq)	Time (Day)	Maintenance (mg eq)	Time (Day)			
150	1	25, 100, 150	8, 36, 64	R092670-PSY-3007	Resubmission	3-Feb-09
None	None	50, 100, 150	1, 8, 36, 64	R092670-PSY-3003	Original Submission	25-Oct-07
None	None	25, 50, 100	1, 8, 36, 64	R092670-PSY-3004	Original Submission	25-Oct-07

Note: All studies were conducted in subjects who had prior experience of paliperidone or passed the tolerability test for paliperidone.

Additionally, the sponsor proposed 1.) a dosing window for patients who cannot receive the injection at the scheduled time, 2.) an alternative dosing regimen for patients who missed paliperidone injection, and (b) (4)

1.1 Objectives

Analysis objective is to identify appropriate initial and maintenance dosing regimen for palieridone long acting injection.

1.1 Methods

4.1.1 Data Sets

Data sets used are summarized in Table 12.

Table 12. Analysis Data Sets

Study Number	Name	Link to EDR
R092670PSY3007	1. pali-3007-11-v2-03jun08-csv.xpt 7. pali-indexexcln-3007set4v5-9jun8-csv.xpt 8. pali-indexexcln-with-3007-8jun8-fullmod-csv.xpt	\\Cdsesub1\evsprod\NDA022264\0026\m5\datasets\population-pk-report-psy3007\analysis\datasets

4.1.2 Software

NONMEM (Double Precision Version 6.1.0, Golobomax Inc.) and S_Plus (Version 7.0, Insightful Inc) were used in the analyses.

1.1 Results

4.1.1 Preview of the Dataset

We used pali-indexexch-with-3007-8jun8-fullmod-csv.xpt as our analysis dataset. There were 19387 PK observations from 1885 subjects in 10 clinical trials, including R092670-USA-3, R092670-INT-11, R092670-INT-12, R092670-PSY-1001, R092670-PSY-1004, R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004, R092670-PSY-3005, and R092670-PSY-3007. PK observations following the administration of three formulations (i.e. Paliperidone Palmitate long-acting injection, Paliperidone ER and IR oral formulations) were pooled together for the population PK analysis.

4.1.2 Population PK analysis

The sponsor's final model included interoccasional variabilities (IOV) on volume of distribution, clearance, and bioavailability. We compared the results for models with and without IOV. The parameter estimates were similar (Table 13)

Table 13 Comparison of Parameter Estimates for Final Model with Interoccational Variability (IOV) and without Interoaccational Variability

Parameters	Model with IOV Value	Model without IOV Value
CL (L/hr)	4.91	5.03
CL-CRCL Power	0.39	0.371
V: Shift Factor for Females	0.83	0.883
V (L)	346	345
V: BMI Power	0.693	0.616
KA: Shift Factor for Females	0.771	0.776
KA: Shift Factof for Deltoid Injection	1.22	1.19
KA * 10^3 (hr-1)	0.52	0.568
KA: Age Power	0.35	0.383
KA: Injection Volume Exponent	0.296	0.288
ALAG1 or D2 (hr)	375	391
F2: Shift Factor for Females	0.846	0.869
F2: Shift Factor for Deltoid Injection	1.37	1.33
F2: Shift Factor Deltoid 1.5 Inch Needle	1.32	1.32
F2	0.197	0.211
F2: BMI Power	0.622	0.705
F2: Injection Volume Exponent	0.231	0.214
IIV CL (CV %)	43.58898944	44.04543109
IIV V (CV %)	75.29940239	84.02380615
IIV KA (CV %)	56.83308895	63.16644679
IIV F2 (SD)	0.360555128	0.626099034
Residual Error (SD)	0.252982213	0.30724583

4.1.3 PK Simulations

The population pharmacokinetic simulations were preformed by using the PK parameter estimates derived from the model without IOV. A Monte-Carlo simulation was performed to evaluate the sponsor proposed dosing regimen. In the simulation, all subjects in Study 3007 who received paliperidone palmitate long-acting injection were "redosed" with different dosing regimens. A total of 258 subjects were included in the simulation. 100 simulations were performed to generate the pharmacokinetic profiles under different dosing scenarios.

- **Evaluation of Maintenance Dosing Regimen:**

We firstly evaluated the sponsor proposed maintenance dosing regimen. The simulated median exposures following 75 mg, 25 mg, and 150 mg q 4 weeks at steady state was compared with the reference exposure (6 mg, 2 mg, and 12 mg q 24 hours at steady state). The results are demonstrated in Figure 22. The recommended maintenance dosing for ER formulation is 6 mg q 24 hours. The simulation showed that 75 mg q 4 week using long-acting formulation yields similar exposure as 6 mg q 24 hour for the ER formulation. Therefore, it is reasonable to choose75 mg q 4 week as the recommended maintenance

dosing from pharmacokinetic point of view. The approved maintenance dosing for the ER formulation is 2 mg-12 mg q 24 hours. Our simulation indicates that 150 mg and 25 mg q 4 weeks lead to similar exposure with 12 mg and 2 mg q 24 hours. Therefore, the sponsor selected maintenance dose appears to be reasonable.

- **Evaluation of Initial Dosing Regimen:**

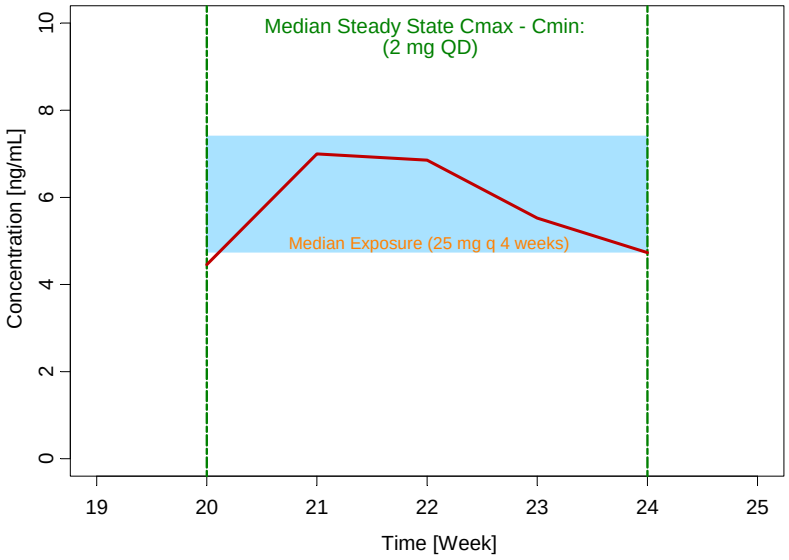
We then evaluated the sponsor proposed initial dosing under different scenarios. The initial doses were given on both Day 1 and by the end of the first week. The maintenance dose was administered starting from the end of the 5th week (Table 14).

In the first scenario, patients who have been receiving a different antipsychotic regimen other than paliperidone or risperidone need to switch to paliperidone long acting injection. The initial paliperidone concentration is zero before the long acting injection is administered. The simulated pharmacokinetic profiles of paliperidone under different initial dosing regimens are shown in Figure 23 A. The reference exposures are the median steady state peak and trough concentrations following 6 mg q.24 hours. dosing. Clearly, if the initial dose is 75 mg, the desirable exposure cannot be achieved after the first month of treatment. Using higher initial dose (e.g. 100 mg and 150 mg), the time needed to achieve the desirable exposure is shortened. Especially, when 150 mg is administered on Day 1, the desirable exposure can be achieved within the first week of treatment, even better than the initial dose of 100 mg. In Study R092670-PSY-3007, patients (about 160 subjects) in one treatment arm received the highest initial dose of 150 mg on both Day 0 and by the end of the first week and then followed by a maintenance dose of 150 mg q 4 week. This dose appears to be safe and well tolerated. The sponsor proposed initial dosing regimen yields lower maximum exposure than the highest initial dosing regimen tested in the trial, while the desirable exposure can be achieved during the first week of treatment. In summary, the sponsor proposed initial dosing regimen appears to be reasonable when a patient switches from a different antipsychotic regimen other than paliperidone or risperidone to paliperidone long acting injection.

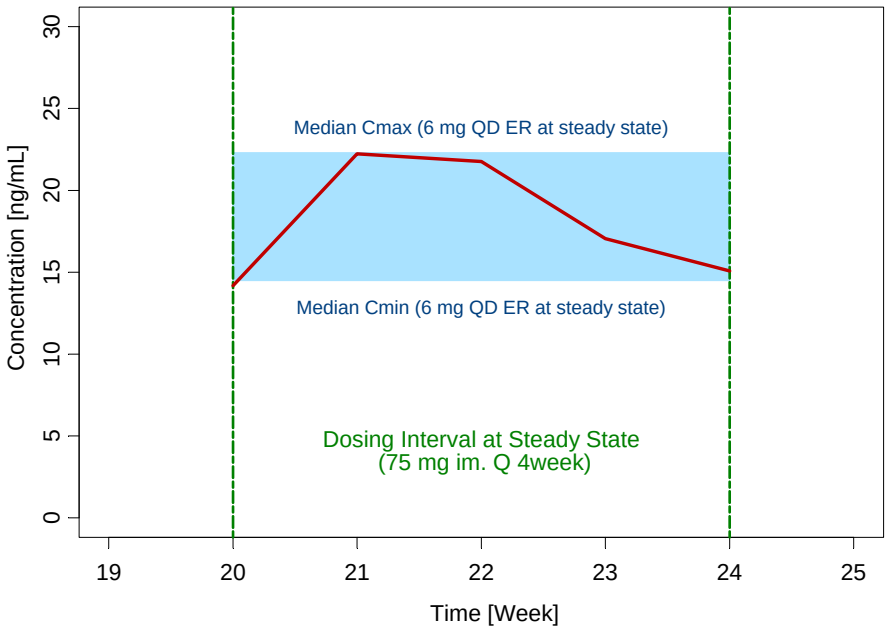
In the second scenario, a patient receiving palieridone ER formulation is switched to paliperidone long-acting injection. The simulation assumes the patient received ER oral formulation and reached steady state prior to the formulation change. The paliperidone initial concentration is equivalent to the median steady state trough concentration by the time paliperidone long acting injection is given. The remaining paliperidone concentration from ER formulation followed exponential decay. According to the label from NDA21999, the terminal half-life for paliperidone ER tablet is 23 hours. The median pharmacokinetic profile following long acting injection was superimposed on top of the remaining palierpeidone concentration from the ER oral formulation. The pharmacokinetic profiles following different initial dosing regimens were thus generated. As shown in Figure 23 B, the exposure in the first week of treatment using the initial dose of 75 mg and 100 mg decreases from the desirable concentration range and cannot return until 1.5-2 weeks later. Following the initial dose of 150 mg, paliperidone exposure

returns to the desirable range in less than 1 week. The peak concentration following the second dose of paliperidone injection is almost not affected by the prior treatment of paliperidone ER oral formulation. In summary, the sponsor proposed initial dosing regimen is acceptable when a patient switches from the paliperidone ER formulation to the long acting injection.

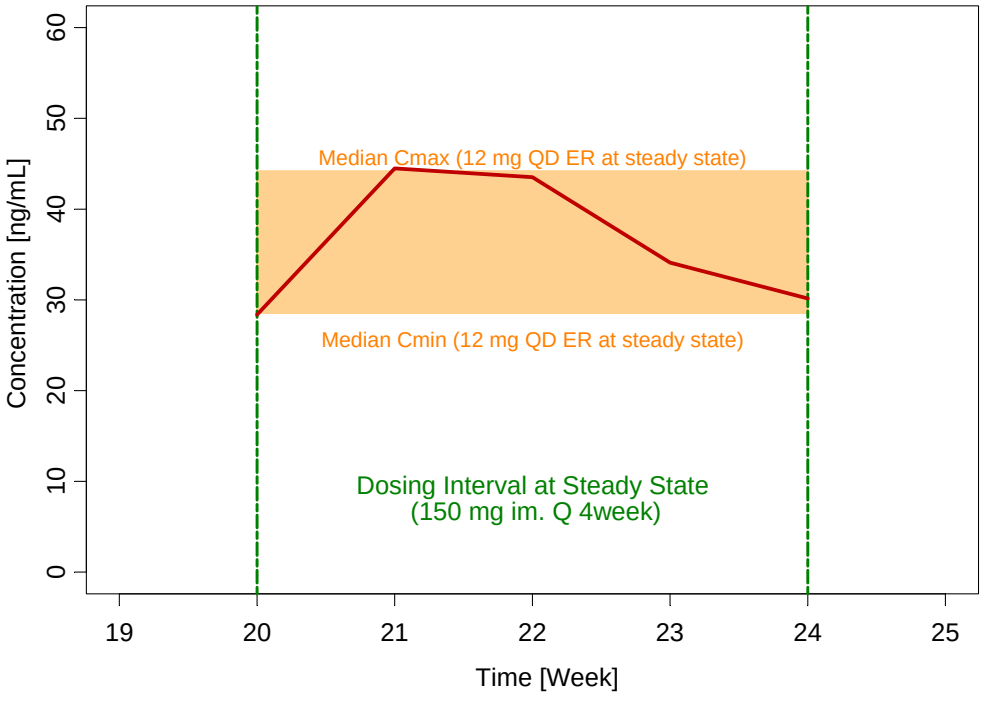
Figure 22 the Simulated Median Exposure following 25 mg (A), 75 mg (B), 150 mg (C) of Long-Acting Injection (Q 4 Weeks) versus the Observed Median Exposure Following 2 mg, 6 mg, and 12 mg (Q24 hour) ER Formulation



(A)


Median Cmax (6 mg QD ER at steady state)
Median Cmin (6 mg QD ER at steady state)
Dosing Interval at Steady State
(75 mg im. Q 4week)
Concentration [ng/mL]
Time [Week]
0
5
10
15
20
25
30
19
20
21
22
23
24
25

(B)


Median Cmax (12 mg QD ER at steady state)
Median Cmin (12 mg QD ER at steady state)
Dosing Interval at Steady State
(150 mg im. Q 4week)
Concentration [ng/mL]
Time [Week]
0
10
20
30
40
50
60
19
20
21
22
23
24
25

(C)

Note: red line= Model predicted steady state median exposure following 25, 75, 150 mg i m. injection every 4 weeks.

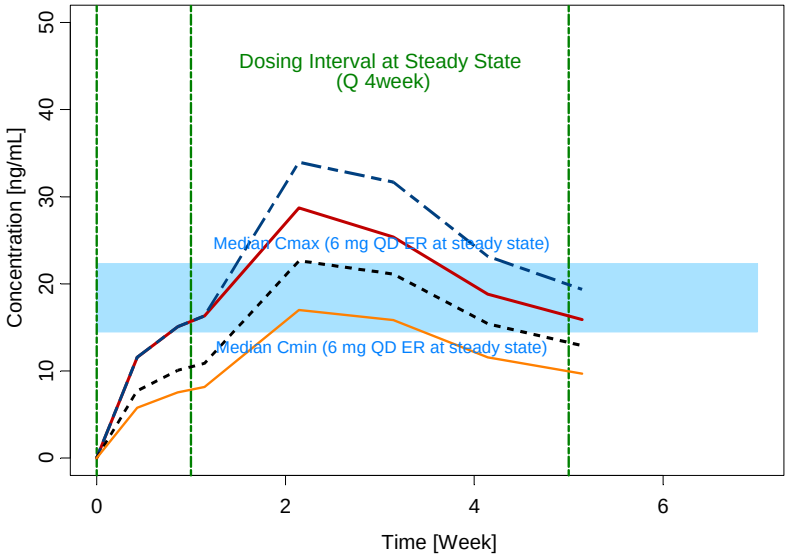
Source:

1. Median Cmax and Cmin at steady state following 6 mg and 12 mg once daily dosing was obtained from Attachment 2.23 in CSR R092670-SCH-01, P-1051 and P-1048.
2. Median Cmax and Cmin at steady state following 2 mg once daily dosing was derived from the 6 mg and 12 mg q 24 hr data based on the linear PK feature of paliperidone.

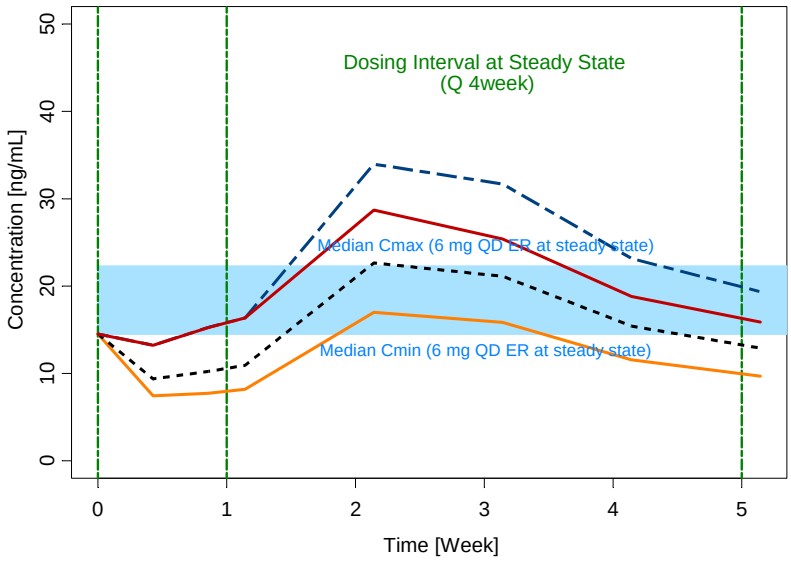
Table 14 Simulated Initial Dosing Regimen

Regimen	Initial Dose	Time
	75	0
1	75	end of the 1st week
	Maintenance Dose	end of the 5th week
	100	0
2	100	end of the 1st week
	Maintenance Dose	end of the 5th week
	150	0
3	100	end of the 1st week
	Maintenance Dose	end of the 5th week
	150	0
4	150	end of the 1st week
	Maintenance Dose	end of the 5th week

Figure 23 Evaluation of Initial Dosing Regimen



(A)



(B)

Note:

A = A patient switches from a different antipsychotic regimen other than paliperidone or risperidone to paliperidone long acting injection.

B = A patient switches from paliperidone ER oral formulation to paliperidone long acting injection

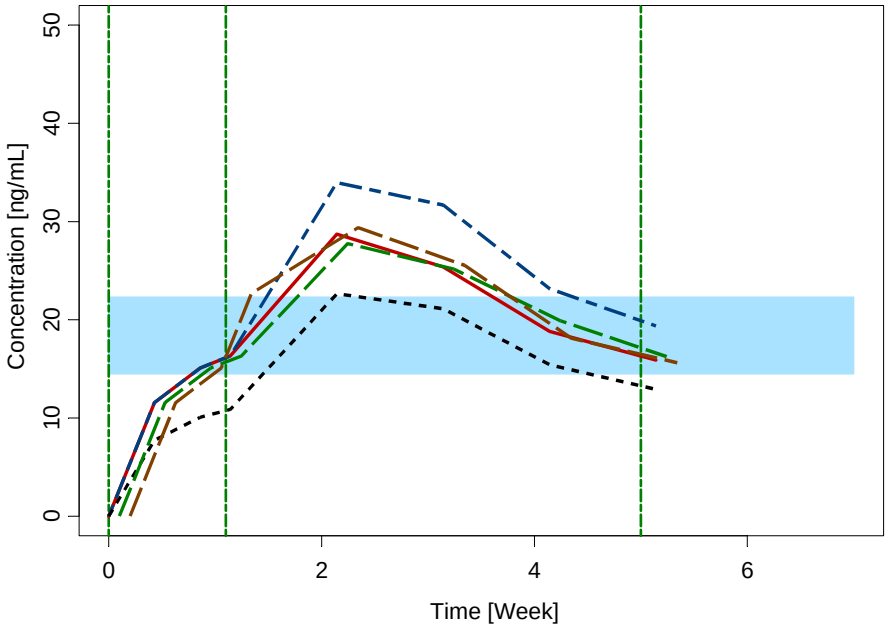
1. Orange solid line = 75 mg on the first day and by the end of the first week
2. Black dashed line = 100 mg on the first day and by the end of the first week
3. Red solid line = 150 mg on the first day and 100 mg by the end of the first week
4. Blue dashed line = 150 mg on the first day and by the end of the first week

- **Evaluation of Dosing Window**

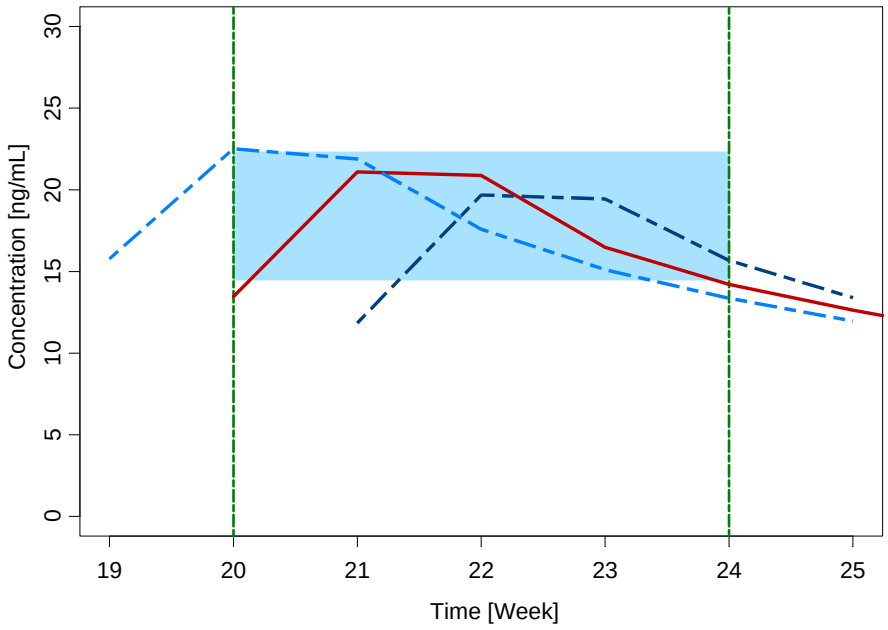
Previous simulations demonstrated that the sponsor proposed initial and maintenance dosing appears to be reasonable. However, in reality, a patient might not receive paliperidone injection following exactly the scheduled time (i.e. the 2nd initial dose by the end of the first week and maintenance dose every 4 weeks). Additional simulations were performed to identify appropriate dosing window within which the paliperidone exposure will not be substantially affected. The first simulation was to identify the dosing window for the 2nd initial dose. The simulation compared the palieridone pharmacokinetic profile when it was given 2 days prior to and 2 days after the scheduled dosing time. The simulation only assumed the paileridone initial concentration was zero, because the pharmacokinetic profile of the second dose was the primary focus. Even under the scenario where the initial palieridone concentration was non-zero, the residual of paliperdione concentration from prior treatment (such as paliperidone ER q 24hr) can be neglected by the time when the 2nd initial dosing window was reached. Simulation results

demonstrated that paliperidone exposure levels were similar if the 2nd initial dose was given within 2 days of the scheduled time (Figure 24 A). The second simulation was conducted to evaluate the dosing window for maintenance dose. A comparison was conducted to evaluate the PK profile when maintenance paliperidone was administered 1 week prior to and after the scheduled time. The results were shown in Figure 24 B. In general, the paliperidone concentrations were within the desired concentration range even when paliperiodne was administered 1 week prior to or after the scheduled time.

Figure 24 Evaluation of Dosing Window



(A)



(B)

Note:

a. Dashed blue line = 150 mg on Day1 and Day 8
Dashed brown line = 150 mg on Day 1 and 100 mg on Day 6
Solid red line = 150 mg on Day 1 and 100 mg on Day 8
Dashed green line = 150 mg on Day 1 and 100 mg on Day 10
Dashed black line = 75 mg on Day 1 and Day 8

b. Dashed light blue line = maintenance dose 75 mg 1 week prior to the scheduled time
Solid red line = maintenance dose 75 mg on the scheduled time
Dashed dark blue line = maintenance dose 75 mg 1 week after the scheduled time

- **Evaluation of Alternative Dosing Regimens for Patients Who Missed Dose**

Additional simulations were conducted to evaluate alternative dosing regimens for a patient who missed the paliperidone dose. If a patient missed the paliperidone dose ≥ 6 month, the pharmacokinetic profile of paliperidone is shown in Figure 25 A. The results demonstrated that if 6 month has elapsed since the last injection, the concentration is almost zero. Therefore, the patient should restart the initial titration dose in order to ensure that the desirable concentration range can be reached within 1 week (Figure 25 A). If a patient missed the paliperidone dose for about 1 month to 6 weeks, the pharmacokinetic profile can be found in Figure 23 B. Paliperidone concentration returned

to the desirable range rapidly following the administration of paliperidone with regular monthly interval (Figure 25 B).

Furthermore, pharmacokinetic simulations were conducted to evaluate the appropriate dosing regimen for a patient who misses doses between 6 weeks to 6 months. The sponsor proposed (b) (4) To evaluate the proposed dosing regimen, the simulations were conducted at two extreme cases. One case is that the first re-initiation dose was given on day 167 (i.e. 24 weeks minus 1 day) since the last injection (Figure 25 C). Paliperidone concentration returned back to the desirable range after the first two consecutive re-initiation doses. Under the second case, the first reinitalization dose was given on Day 43 (i.e., 6 weeks plus 1 day) after the previous injection. The pharmacokinetic profile was shown on Figure 25 D. The median peak concentration following the sponsor's proposal was 23% higher than the median maximum concentration using correspondent paliperidone ER formulation.

The 23% increase in exposure does not lead to safety concern if the patient is stabilized at a dose less than or equal to 100 mg eq, because the overall exposure is still below the highest clinical tested exposure. However, the following example demonstrates how this proposal can lead to potential safety concern. (b) (4)

We recommend the re-initiation dose for a patient who misses dose for 6 weeks – 6 months should not exceed 100 mg. Following our recommendation, the simulated pharmacokinetic profiles were shown in Figure 4 E and F. Paliperidone concentration will not exceed the highest median exposure observed in the trial. In the mean time, paliperidone exposure returns to the desirable concentration in less than 2-3 dosing cycles.

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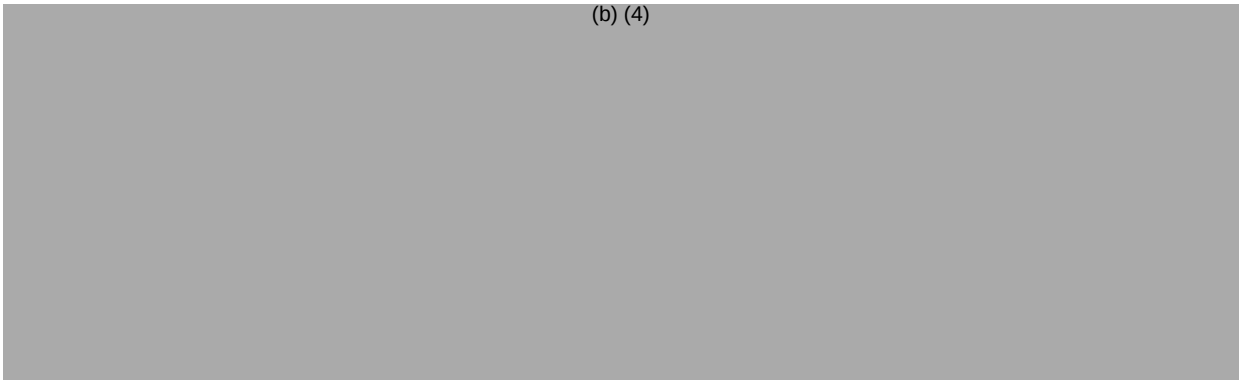


Solid red line = Median PK Profile.

Blue Shaded Area =Median Cmax and Cmin at steady state following 6 mg once daily dosing. (Obtained from Attachment 2.23 in CSR R092670-SCH-01, P-1051)

Brown Shaded Area = Median Cmax and Cmin at steady state following 12 mg once daily dosing.

(Obtained from Attachment 2.23 in CSR R092670-SCH-01, P-1051)

(b) (4)

- Evaluation of paliperidone dosing regimen for patients with mild renal impairment (Creatinine clearance ≥ 50 mL/min to < 80 mL/min)

Paliperidone is mainly excreted through kidney, with 59% of the dose excreted unchanged into urine. The sponsor's population PK analysis confirmed that creatinine clearance is a significant covariate for paliperidone clearance. Therefore, for a patient with compromised renal function, paliperidone exposure will be increased if the dose is not adjusted accordingly.

We conducted simulations to identify appropriate dosing regimen of paliperidone palmitate in patients with mild renal impairment (50 mL/min ≤creatinine clearance < 80 mL/min). Paliperdione palmitate is not recommended in patients with moderate and severe renal impairment. Our simulation was conducted based on the sponsor's population PK model. The model was derived from PK samples in patients with various creatinine levels (Figure 26). A total of 188 subjects (9.9%) whose creatinine clearance between 50 mL/min to 80 mL/min were included in the population PK modeling. The simulation included subjects from Study 3007, with their creatinine clearance values assumed to be 50 mL/min. The simulation was performed 100 times and the median exposure was obtained for comparison.

The sponsor proposed maintenance dose is 50 mg q 4 weeks for patients with mild renal impairment (50 mL/min ≤ creatinine clearance < 80 mL/min). Our simulation was conducted in patients with creatinine clearance of 50 mL/min. Following the sponsor proposed maintenance dosing regimen, paliperidone concentration profile is shown in Figure 27. The steady state concentration is within the desirable concentration range.

(b) (4) Following the sponsor proposed dose, the pharmacokinetic profile of paliperidone is shown in Figure 28. Even though the peak concentration following the sponsor proposed initial dosing is above the desirable exposure range, the overall exposure is still below the highest clinical tested exposure level (150 mg on both Day 1 and Day 8).

Figure 26 Distribution of Creatinine Clearance in Population PK Dataset

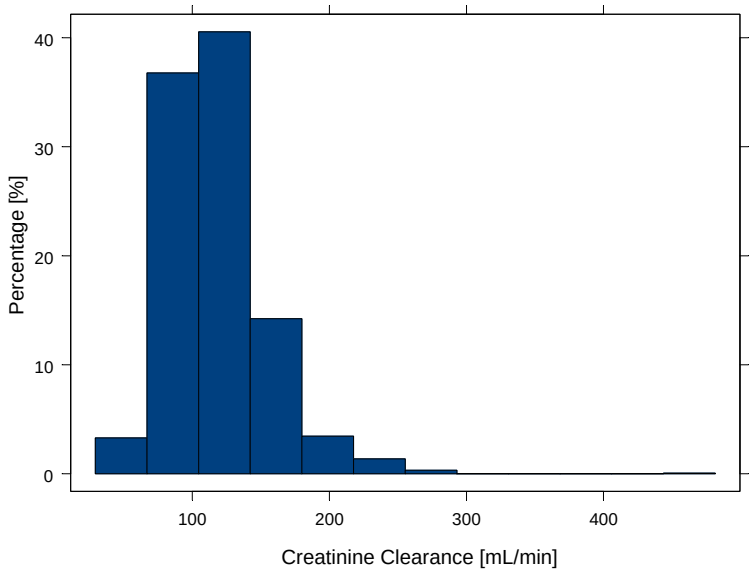
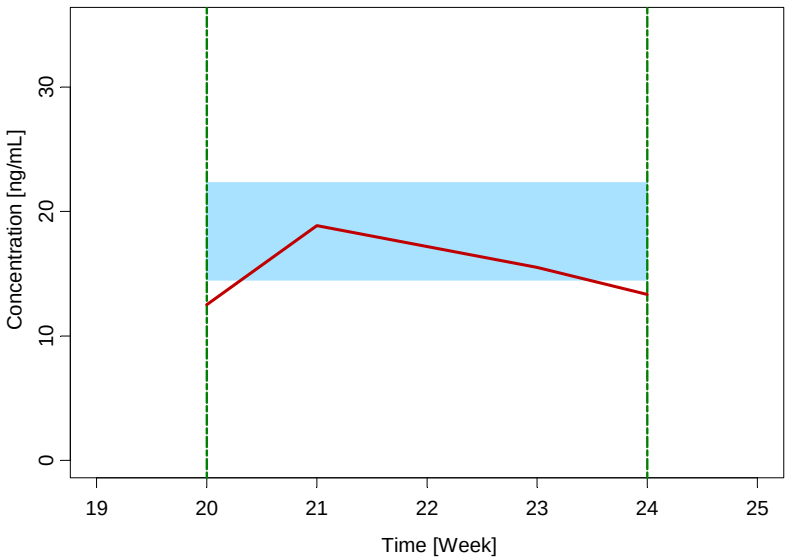


Figure 27 Pharmacokinetic Profile of Palieridone at Steady State Following 50 mg q Paliperidone Palmitate Long Acting Injection q 4 Weeks in Patients with Mild Renal Impairment (CRCL = 50 mL/min)



Note: Solid red line = Median PK Profile.

Shaded Area =Median Cmax and Cmin at steady state following 6 mg once daily dosing was obtained from Attachment 2.23 in CSR R092670-SCH-01, P-1051

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
		Palieridone_NDA22264_HZ\ppk Analyses

4.2 Analytical Review:

Title (BA1113): Validation (partial) of an LC-MS/MS method for the determination of Paliperidone (JNJ 16232411) in human heparin plasma

The sponsor included in this submission a partial validation of the LC/MS/MS used to determine Paliperidone concentrations in plasma. The following tables provide the validation and controls for the determination of Paliperidone (JNJ-1623411) in plasma. The assay procedure is acceptable

Partial validation JNJ-16232411					
Intra-run Bias [%]		0.100	ng/mL	-1.5	Table 1
		0.250	ng/mL	2.4	
		5.20	ng/mL	3.5	
		185	ng/mL	0.5	
Intra-run CV [%]		0.100	ng/mL	7.1	Table 1
		0.250	ng/mL	2.4	
		5.20	ng/mL	1.6	
		185	ng/mL	3.1	
Inter-run Bias [%]		0.100	ng/mL	-2.8	Table 1
		0.250	ng/mL	0.8	
		5.20	ng/mL	4.4	
		185	ng/mL	2.7	
Inter-run CV [%]		0.100	ng/mL	5.8	Table 1
		0.250	ng/mL	4.0	
		5.20	ng/mL	2.4	
		185	ng/mL	3.3	
Selectivity	interference ≤20.0% for analyte	6 out of 6 plasma sources			Table 3
	interference ≤ 5.0% for internal standard	6 out of 6 plasma sources			Table 3
Validated concentration range (undiluted samples)		0.100 ng/mL~250 ng/mL			Table 2
Matrix effect(% CV)		0.200	ng/mL	6.3	Table 4
		250	ng/mL	2.3	

Stability

Processed sample stability	94 h in autosampler set at 4℃	Table 5

Table 1: Accuracy and precision in quality control samples spiked with JNJ-16232411 in human heparin plasma.

Run Date	Curve Numbe	QC LLOQ 0.100 ng/mL	%Bias	QC Low 0.250 ng/mL	%Bias	QC Medium 5.20 ng/mL	%Bias	QC High 185 ng/mL	%Bias
01-Feb-2008	1	0.0958	-4.2	0.254	1.6	5.35	2.9	184	-0.5
		0.0897	-10.3	0.255	2.0	5.34	2.7	184	-0.5
		0.0982	-1.8	0.246	-1.6	5.39	3.7	195	5.4
		0.111	11.0	0.257	2.8	5.35	2.9	180	-2.7
		0.0969	-3.1	0.260	4.0	5.29	1.7	183	-1.1
		0.0996	-0.4	0.264	5.6	5.54	6.5	192	3.8
Intrarun Mean		0.0985		0.256		5.38		186	
Intrarun SD		0.00700		0.00610		0.0862		5.82	
Intrarun %CV		7.1		2.4		1.6		3.1	
Intrarun %Bias		-1.5		2.4		3.5		0.5	
n		6		6		6		6	
02-Feb-2008	2	0.0875	-12.5	0.267	6.8	5.26	1.2	187	1.1
		0.0966	-3.4	0.255	2.0	5.70	9.6	195	5.4
		0.0877	-12.3	0.258	3.2	5.44	4.6	190	2.7
		0.0993	-0.7	0.251	0.4	5.62	8.1	193	4.3
		0.0968	-3.2	0.246	-1.6	5.59	7.5	203	9.7
		0.101	1.0	0.269	7.6	5.51	6.0	198	7.0
Intrarun Mean		0.0948		0.258		5.52		194	
Intrarun SD		0.00582		0.00898		0.156		5.72	
Intrarun %CV		6.1		3.5		2.8		2.9	
Intrarun %Bias		-5.2		3.2		6.2		4.9	
n		6		6		6		6	
02-Feb-2008	3	0.0996	-0.4	0.253	1.2	5.37	3.3	182	-1.6
		0.0940	-6.0	0.235	-6.0	5.31	2.1	196	5.9
		0.0994	-0.6	0.237	-5.2	5.24	0.8	190	2.7
		0.104	4.0	0.245	-2.0	5.56	6.9	185	0.0
		0.0935	-6.5	0.235	-6.0	5.47	5.2	188	1.6
		0.0989	-1.1	0.250	0.0	5.39	3.7	194	4.9
Intrarun Mean		0.0982		0.243		5.39		189	
Intrarun SD		0.00393		0.00794		0.114		5.31	
Intrarun %CV		4.0		3.3		2.1		2.8	
Intrarun %Bias		-1.8		-2.8		3.7		2.2	
n		6		6		6		6	
Mean Concentration F		0.0972		0.252		5.43		190	
Inter-run SD		0.00565		0.0101		0.132		6.28	
Inter-run %CV		5.8		4.0		2.4		3.3	
Inter-run %Bias		-2.8		0.8		4.4		2.7	
n		18		18		18		18	

Table 3a: Selectivity of JNJ-16232411 based on the LLOQ samples

Run Date	Curve Number	6 sources 0.100 ng/mL	%Bias
01-Feb-2008	1	0.0930	-7.0
		0.0919	-8.1
		0.0999	-0.1
		0.0947	-5.3
		0.108	8.0
		0.111	11.0
Mean		0.100	
S.D.		0.00809	
%CV		8.1	
%Accuray		100.0	
%Bias		0.0	
n		6	

Table 5: Stability of JNJ-16232411 in processed human heparin plasma samples (QCs samples).

Run Date	Injection Times	QC Low 0.250 ng/mL	%Bias	QC Medium 5.20 ng/mL	%Bias	QC High 185 ng/mL	%Bias
01-Feb-2008	1st	0.254	1.6	5.35	2.9	184	-0.5
		0.255	2.0	5.34	2.7	184	-0.5
02-Feb-2008	2nd	0.248	-0.8	5.41	4.0	192	3.8
(25 hours)		0.261	4.4	5.31	2.1	191	3.2
03-Feb-2008	3rd	0.258	3.2	5.29	1.7	192	3.8
(49 hours)		0.275	10.0	5.41	4.0	189	2.2
05-Feb-2008	4th	0.239	-4.4	5.26	1.2	183	-1.1
(94 hours)		0.252	0.8	5.54	6.5	190	2.7

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hao Zhu
7/22/2009 04:08:57 PM
BIOPHARMACEUTICS

Kofi Kumi
7/22/2009 04:15:19 PM
BIOPHARMACEUTICS

Raman Baweja
7/22/2009 04:51:15 PM
BIOPHARMACEUTICS

Yaning Wang
7/22/2009 05:21:44 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA#:	**22264**
Submission Date:	10/26/2007, 2/25/2008
Brand Name:	Invega Sustenna
Generic Name:	Paliperidone palmitate
Formulation:	ER suspension for IM Injection
Strength:	Prefilled syringe 25, 50, 75, and 100 mg eq.
Sponsor:	Johnson and Johnson
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Recommendation

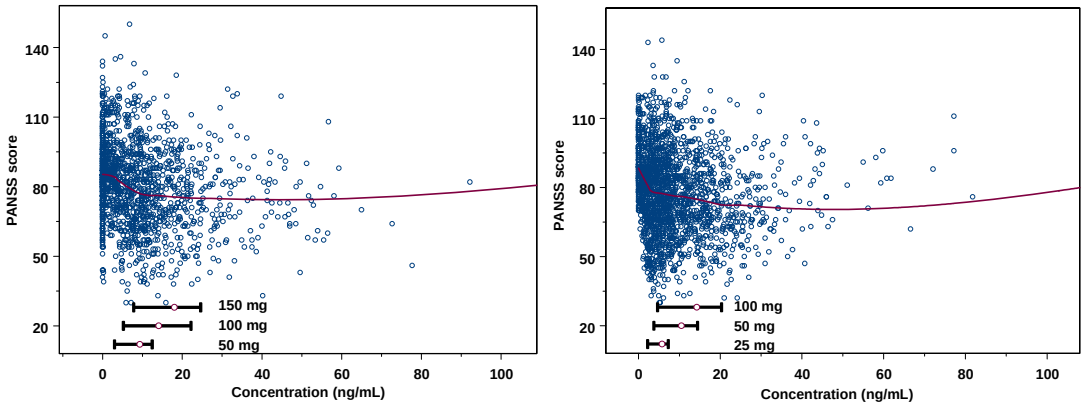
OCP finds this NDA is acceptable. The following comments and the labeling recommendations are being sent to Clinical Division for consideration.

Comments to the medical officer

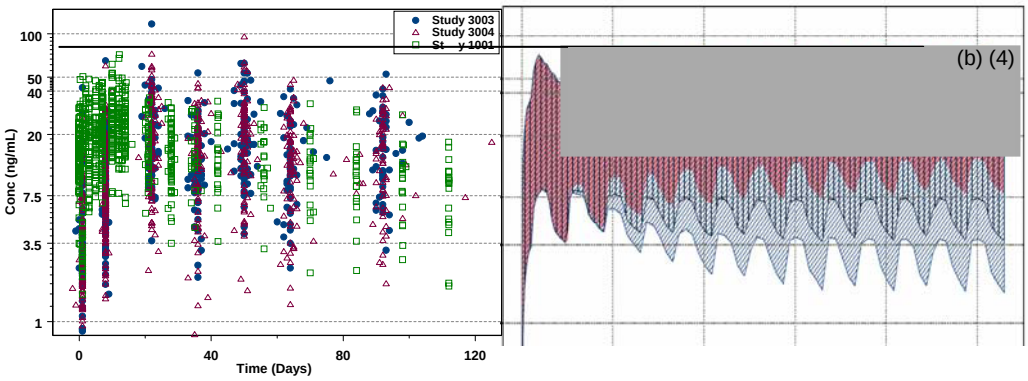
1. The proposed paliperidone palmitate dosing is a dose of (b) (4) mg eq. administered in the deltoid muscle on treatment days 1 and 8, followed by a monthly (every 4 weeks) dose within the dose range of 25 – 100 mg eq. administered in either the deltoid or gluteal muscle. For deltoid administration, a 1.5-inch needle is proposed to be used for patients >=90 kg and a 1-inch needle for patients <90 kg. The proposed initiation dosing regimen, i.e. administration to deltoid muscle, has not been studied in Phase 3 efficacy trials. The applicant performed various simulations of PK profiles to support the proposed initiation of treatment. Our evaluations take the following aspects into consideration.

    - Quicker achieving of therapeutic concentration is beneficial for disease control. Initial deltoid injection, which facilitates a rapid attainment of potential therapeutic concentrations, is a better choice compared to gluteal injection.

    - As shown in the following figures, when the concentrations increase initially, PANSS scores decrease considerably; while as the concentrations increase further, the PANSS scores do not change to a large extent (left panel for Study 3003 and right for 3004). Indicated by the bars at the bottom of the figures showing the concentration ranges (from 25 percentile to 75 percentile with the means as empty circles on the bars) for different doses used in the trials, the concentrations generated by 100 mg gluteal injection used in Study 3003 and 3004 are in the appropriate ranges.



- Compared to the fixed dose studies 3003 and 3004 (shown in the left panel), the proposed initial dosing regimen (pink area in the right panel) may generate higher exposures as shown in the following figure.



- Compared to the recommended dose for paliperidone ER tablets (6 mg QD, maximum dose of 12 mg QD), the currently proposed initial dosing regimen for injection may generate exposures comparable to that of 7.5 mg ER tablets QD dosing, which is 24%-34% higher than the 6 mg QD dosing, although it is lower than that of the maximum recommended oral ER tablets 12 mg QD dosing as shown in the following tables.

PK parameters of paliperidone ER tablets at Day 14 after 9 mg QD dose (n=32)

Cmin,ss ng/mL	Cmax,ss ng/mL	tmax,ss h	AUCτ,ss, ng.h/mL	Cavg,ss, ng/mL	Cmax,ss: Cmin,ss Ratio	CL/F mL/min
25.3 ± 16.2 (63.8) 3.86 - 76.9 [21.7]	40.2 ± 24.1 (59.9) 8.79 - 130 [35.0]	10.90 ± 8.88 (81.4) 1.87 - 24.00 [8.99]	762 ± 464 (60.9) 173 - 2331 [638]	31.7 ± 19.3 (60.9) 7.19 - 97.1 [26.6]	1.69 ± 0.49 (28.8) 1.15 – 3.07 [1.6]	274 ± 169 (61.6) 64.4 - 869 [235]

PK parameters after the second deltoid injection of 100 mg eq paliperidone

N	Cmax,ss ng/mL	tmax h	AUCτ* ng·h/mL	Cavg ng/mL	FI (%)
22	31.3 (15.8-67.4)	9.95 (6.94-20.86)	14728 (8253-26453)	21.9 (12.3-39.5)	88.6 (57.8-138)

* AUC during 28 days, convert to AUC24h=526 ng·h/mL

- Considering the importance of initial exposure, initial deltoid injection may be beneficial for quicker achieving of desired efficacy. However, compared to the exposure obtained by oral ER paliperidone at recommended dose of 6 mg (median Cmax 23.3 ng/mL, AUC24h 425 ng·h/mL, values obtained from 9 mg data assuming linear kinetics), the exposure of proposed initial dosing regimen is 24-34% higher. Further, the clinical studies indicate that the 100 mg gluteal injection is efficacious and therefore the question is not whether the 100 mg deltoid administration will be effective. Instead the concern is regarding the safety of the 100 mg deltoid injection where higher levels were seen compared to corresponding gluteal injections. Therefore, the deltoid injection dose should be

reduced by 20-26%, and the most feasible next lower for deltoid administration is 75 mg eq.

2. After the initial two injections, the criteria for selection from 25-100 mg eq doses are not clear. The applicant should set the criteria and put it in the label. When setting the criteria, body weight (or BMI) and renal function should be considered among other factors.

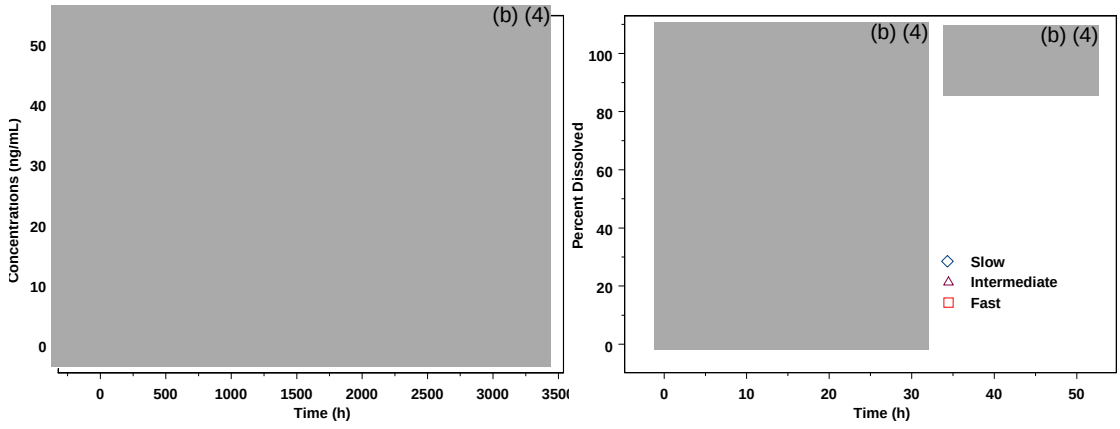
3. For renally impaired patients, the total exposure (AUC and Cmax) will be increased significantly compared to subjects with normal renal function. The half-life will also be increased, resulting in delayed achievement of steady state. Therefore, the applicant's proposal is reasonable for not using in patients with moderate and severe renal impairment. For patients with mild renal impairment, the dose should be reduced (from 75 mg to 50 mg).

Comments to the review chemist

1. The IVIVC model is established. However, please note that the relationship was built using three batches (slow, intermediate, and fast with particle sizes d50 of (b) (4) µm, (b) (4) µm, and (b) (4) µm, respectively) and when the extra slow batches (d50 (b) (4) µm) is included, the IVIVC did not exist.

2. The IVIVC for the long-acting injection was established on the basis of variation in the particle size of the drug, and not on the basis of changes to the release-rate mechanism excipients as is seen with oral modified release dosage forms.

3. In vivo data for buiding the model had large variability as shown in the following figure (left panel) although the in vitro variability is small (right panel). When setting the release specifications and other applications of the model, this should be taken into considerations.



4. The in vitro release specifications proposed by the applicant are acceptable as summarized in the following table.

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1.2 Summary of important clinical pharmacology findings

This submission is an original New Drug Application (NDA) for paliperidone palmitate [redacted] (b) (4) for the treatment of schizophrenia and the prevention of recurrence of symptoms of schizophrenia. Paliperidone has been marketed as an extended release (ER) formulation with a once-daily administration schedule for the treatment of schizophrenia (INVEGA™). Based on agreements between FDA and the applicant, results from studies with oral paliperidone ER were used to support the PK of paliperidone after administration of paliperidone palmitate in special populations and the drug-drug interaction potential. No specific studies were performed with paliperidone palmitate. This summary involves the newly conducted studies.

Single dose study

The following table shows the PK parameters after a single dose from 25 mg eq to 150 mg eq at different injection sites (study R092670-PSY-1004).

	Deltoid											
	25 mg eq.			50 mg eq.			100 mg eq.			150 mg eq.		
PK parameter	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median
t_{max}, days	22	14.69 (9.81)	13.01	23	15.04 (9.63)	13.00	22	17.27 (13.67)	12.51	21	16.58 (10.13)	14.00
C_{max}, ng/mL	22	5.88 (2.31)	5.46	23	10.4 (6.23)	8.79	22	13.4 (7.82)	10.7	21	29.2 (11.8)	27.5
AUC_{last}, ng.h/mL	22	5540 (1831)	5100	19	10033 (4547)	9445	22	16260 (6579)	15484	17	30273 (7625)	28731
AUC_{∞}, ng.h/mL	20	6074 (1942)	5724	18	11800 (4579)	11162	16	20069 (7778)	18675	18	36883 (11095)	33538
$t_{1/2}$, days	20	25.5 (10.2)	24.9	18	33.29 (16.55)	29.06	16	45.7 (16.1)	43.7	18	38.0 (10.6)	40.6
	Gluteal											
	25 mg eq.			50 mg eq.			100 mg eq.			150 mg eq.		
PK parameter	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median
t_{max}, days	21	19.00 (14.12)	16.00	24	16.70 (10.66)	13.41	25	20.55 (13.25)	14.12	24	23.17 (17.68)	17.03
C_{max}, ng/mL	21	4.89 (2.10)	4.35	24	7.82 (3.28)	6.85	25	12.6 (7.04)	10.7	24	17.9 (9.52)	15.2
AUC_{last}, ng.h/mL	20	4653 (1784)	4771	21	9236 (2417)	8978	21	14520 (7645)	11907	20	23546 (8700)	21984
AUC_{∞}, ng.h/mL	19	5308 (1850)	5435	19	10556 (2039)	10088	18	19674 (8478)	19297	16	30415 (9287)	31344
$t_{1/2}$, days	19	27.1 (15.1)	25.1	19	34.1 (14.3)	31.2	18	40.6 (10.4)	40.0	16	47.5 (19.8)	49.1

Multiple dose study

A summary of the PK parameters of paliperidone after i.m administration of 100 mg paliperidone palmitate (on Days 1, 8, 36 and 64), in the deltoid and gluteal muscle is given in the following Table (study R092670-PSY-1001).

	Second i.m. injection				Fourth i.m. injection			
	Deltoid		Gluteal		Deltoid		Gluteal	
Parameter	n	Median (min - max)	n	Median (min - max)	n	Median (min - max)	n	Median (min - max)
t_{max} (days)	22	9.95 (6.94 – 20.86)	24	10.02 (6.94 – 21.08)	21	4.99 (1.13 – 13.96)	24	6.54 (0.98 – 20.12)
C_{max} (ng/mL)	22	31.3 (15.8 – 67.4)	24	24.1 (9.10 – 50.2)	21	23.7 (8.27 – 71.6)	24	22.3 (6.44 – 56.1)
AUC_{τ} (ng.h/mL)	22	14728 (8253 – 26453)	24	12108 (4736 – 24754)	20	12946 (4287 – 27621)	23	11021 (3198 – 26749)
C_{avg} (ng/mL)	22	21.9 (12.3 – 39.5)	24	18.0 (7.06 – 36.8)	20	19.2 (6.38 – 42.6)	23	16.4 (4.76 – 41.3)
FI (%)	22	88.6 (57.8 – 138)	24	94.8 (53.2 – 160)	20	71.9 (32.6 – 177)	23	56.2 (40.7 – 107)

Dose proportionality

The total exposure (AUC∞) of paliperidone increased proportionally with dose after single-dose injections of 25 to 150 mg eq. paliperidone palmitate in both the deltoid and gluteal muscle. The increase in Cmax was less than dose proportional for both injections sites at doses greater than 50 mg eq. The Cmax of paliperidone was generally higher after single-dose injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (geometric mean ratio ranging from 108.75% to 164.85%) whereas the difference was less pronounced for AUC∞ (study R092670-PSY-1004).

Effect of injection sites

Injection of paliperidone palmitate in the deltoid or the gluteal muscle has been compared in three Phase 1 clinical trials with extensive PK sampling (R092670-USA-3, R092670-PSY-1001, and R092670-PSY-1004) and in one Phase 3 trial with sparse sampling (R092670-PSY-3005). Injection of paliperidone palmitate in the deltoid muscle consistently resulted in higher plasma concentrations compared to injections in the gluteal muscle. The observed Cmax and AUC were 20-50% higher after injection in the deltoid muscle compared to the gluteal muscle.

IVIVC

A Level A in vitro-in vivo correlation (IVIVC) model was established for paliperidone palmitate formulations with different release rate profiles. This IVIVC model was validated by establishing internal and external predictability. The internal validation of the IVIVC model was demonstrated with mean absolute % prediction error (% PE) criteria for AUCt and Cmax of less than 8% and individual absolute % PE less than 12%. External validation of the IVIVC model was within the 10% limit for Cmax and AUCt. However, when including the extra slow batches (d50 (b) (4) µm) in the data, the IVIVC did not exist. In addition, the in vivo variability is much larger than the in vitro variability. The in vitro release specifications were set based on the IVIVC model.

Population PK study

A population PK analysis was conducted using sparse PK samples from the Phase 3 studies combined with full plasma concentration-time profiles from a selection of Phase 1/2 studies to evaluate the importance of different covariates. Evaluation of subject covariates demonstrated that absorption-related parameters depended both on subject demographic characteristics and on injection-related covariates. The influence of gender, age, injection volume, and injection site on KA was significant. Similarly, gender, body mass index (BMI), needle length, injection sites and injection volume had a statistically significant influence on F2. Moreover, CL was related to creatinine clearance (CRCL), while V was related to BMI and gender.

Simulation scenarios with the statistically significant covariates from the population PK analysis revealed that compared to deltoid injections, repeated administration in the

gluteal muscle resulted in a delayed time to achieve steady-state (~ 4 wk longer). Deltoid injections resulted in a faster rise in initial plasma concentrations, facilitating a rapid attainment of potential therapeutic concentrations.

Higher doses associated with larger injection volumes increased the apparent half-life of paliperidone, which in turn increased the time to achieve steady-state.

Needle length was an important variable for the absorption kinetics from the deltoid injection-site. Simulations indicated that the use of a longer needle in the deltoid muscle for the heavy individuals might be associated with an initial faster release of paliperidone into the systemic circulation, which could help overcome the slower absorption observed in heavier individuals described below.

The body size variable BMI was another important covariate for paliperidone palmitate. A slower rise in initial concentrations was observed in the obese population, which possibly occurred due to the reduced speed of initial influx from the injection site. Initiating the first two injections in the deltoid muscle and using a longer 1.5-inch needle for deltoid injection in heavy subjects can mitigate this effect. These observations are consistent with the expectation that in heavy subjects, administration into the adipose layer of the deltoid muscle can be avoided with the use of a longer injection needle.

Renal function was an important covariate influencing the PK of paliperidone. Simulations indicate that a 75 mg eq. dose in subjects with mild renal impairment (CRCL: 50-80 mL/min) resulted in a similar exposure as a 100 mg eq. dose in subjects with normal renal function (CrCL >80 mL/min). This may therefore form the basis for dose adjustment in renally impaired subjects.

Age (on KA) and gender (on KA, F2, and V) were two subject related variables that were statistically significant in the covariate analysis. However, simulations indicate that their influence on systemic exposure was too small to be of clinical relevance.

Since the results from studies with oral paliperidone ER were used to support the PK of paliperidone after administration of paliperidone palmitate in special populations and no specific studies were performed with paliperidone palmitate, the population PK study is used to confirm the covariate effects.

_____ _____

John Duan, Ph.D. Date
Reviewer
Division of Clinical Pharmacology 1

_____ _____

Raman Baweja, Ph.D. Date
Team Leader
Division of Clinical Pharmacology 1

cc: HFD-130 NDA 22264
HFD-860 Mehul Mehta, Ramana Uppoor, Raman Baweja, John Duan

Briefing: July 31, 2008, 1:30 to 2:30 pm

Briefing Attendees: Drs. Thomas Laughren, Mitchell Mathis, Gwen Zornberg, Jing Zhang, Gil Burckhardt, Suresh Doddapaneni, Ramana Uppoor, Barry Rosloff, Silvana Borges, Aisar Atrakchi, Elzbieta Chalecka-Franazek, Dennis Bashaw, Brian Booth, Raman Baweja, John Duan

2. QUESTION BASED REVIEW

1. What are the proposed mechanisms of action and therapeutic indications?

This is an original New Drug Application (NDA) for paliperidone palmitate (b) (4) for the treatment of schizophrenia and the prevention of recurrence of symptoms of schizophrenia. Currently, INVEGA™ (paliperidone) Extended-Release Tablets are approved for the acute and maintenance treatment of schizophrenia.

Paliperidone palmitate is hydrolyzed to paliperidone. Paliperidone is the major active metabolite of risperidone. The mechanism of action of paliperidone is unknown, but it has been proposed that the drug's therapeutic activity in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

2. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

The active ingredient, paliperidone palmitate, is a psychotropic agent belonging to the chemical class of benzisoxazole derivatives.

Paliperidone palmitate is very slightly soluble in ethanol and methanol, practically insoluble in polyethylene glycol 400 and propylene glycol, and slightly soluble in ethyl acetate. Paliperidone palmitate doses are expressed as milligram equivalents (mg eq.) to paliperidone (e.g., paliperidone palmitate 156 mg corresponds to paliperidone 100 mg, noted as 100 mg eq.). Paliperidone is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in dose strengths of 25, 50, 75, and 100 mg eq. It is provided in a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper and tip cap (bromobutyl rubber). The retail kit contains 2 safety needles (a 1 ½-inch 22 gauge safety needle and a 1-inch 23 gauge safety needle). (b) (4)

3. What are the proposed dosage and route of administration?

The proposed initiation of paliperidone is with a dose of (b) (4) eq. administered in the deltoid muscle on treatment days 1 and 8, followed by a monthly (every 4 weeks) dose within the dose range of (b) (4) eq. based on individual patient factors. The monthly doses (following the day 8 dose) can be administered in either the deltoid or gluteal muscle.

4. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Paliperidone has been marketed as an extended release (ER) oral tablet formulation with a once-daily administration schedule for the treatment of schizophrenia (INVEGA™).

Non-adherence to antipsychotic medication is one of the problems in the long-term treatment of schizophrenia and other psychiatric disorders. Therefore, paliperidone was also developed as an ER suspension for i.m. injection.

The pharmacokinetics of i.m. injections of paliperidone palmitate have been characterized in 3 clinical pharmacology and 7 biopharmaceutics studies in subjects with schizophrenia or schizoaffective disorder, a Phase 2 study in subjects with schizophrenia, and in a Phase 1 study in Japanese subjects with schizophrenia. In the Phase 3 studies, sparse PK sampling was included and used for the population PK evaluation of paliperidone after i.m. injection of paliperidone palmitate. For most repeated dosing studies, paliperidone palmitate was injected on Day 1 and Day 8, followed by monthly injections.

For all studies in the development program of paliperidone palmitate, the study population consisted of otherwise healthy subjects with schizophrenia, who represent the target population for the use of this ER suspension of paliperidone palmitate for i.m. injection. In some studies, also subjects with related conditions, like schizophreniform or schizoaffective disorder, were allowed to participate. In general, prolonged use of antipsychotics is not well tolerated in healthy subjects. Therefore, the prolonged exposure inherent to the use of a long-acting injectable is not justified in healthy subjects. The study population in the Phase 1 program was thus largely representative for the population studied in Phase 3.

In the initial studies, paliperidone palmitate formulations that differed in particle size and/or solvent composition were used for the exploration of the formulation characteristics that result in a pharmacokinetic profile to support once monthly dosing and optimal pharmaceutical stability. Subsequently, the development was focused on the final to-be-marketed (TBM) formulation, which was also used in the Phase 3 safety and efficacy studies.

The safety and tolerability of paliperidone palmitate injections in the gluteal muscle and the PK properties after single and multiple dosing were initially investigated in Phase 1 clinical studies, using different pilot formulations of paliperidone palmitate (Studies R092670-BEL-1, R092670-BEL-2, and R092670-BEL-4,). The F004 formulation was identified as having the most optimal PK characteristics for a once-monthly dosing regimen, and the formulation was then scaled up and improved to the F011 formulation. The relative bioavailability of the F011 compared to the F004 formulation after single and multiple dosing was assessed in Study R092670-INT-11, and the dose-proportionality of the F011 formulation was evaluated in Study R092670-INT-12. Formulation F011 was chosen to be used for Phase 2 and 3 clinical studies. Later on, to improve the impurity profile of the product, the sterilization technique of the drug substance was changed from (b) (4) to (b) (4) During the Phase 3 efficacy and safety studies, formulation F011 was further optimized to improve the storage conditions. (b) (4) This formulation is identified as the TBM formulation F013. (b) (4)

characteristics of F011 and F013 are identical. Both the F011 and the F013 formulation have been used during the Phase 3 development of paliperidone palmitate. The TBM formulation (F013) was used in all Phase 3 efficacy and safety studies. Phase 1/2 formulation F011* (* referred to the formulation used in phase 1/2, drug substance (b) (4) was used in Phase 2 Study R092670-SCH-201 and formulation F011 was included in three Phase 3 studies (R092670-PSY-3001, R092670-PSY-3002, and R092670-PSY-3004). All 3 formulations (F011*, F011, F013) were tested in the biopharmaceutics studies. The comparability and relative bioavailability of the F011 and F013 formulation have been shown in the Phase 1 Study R092670-PSY-1002 and in the population PK analysis. The dose-proportionality of the F013 formulation was assessed in Study R092670-PSY-1004.

Paliperidone palmitate will be supplied as a sterile aqueous suspension (eq. 100 mg/mL) for i.m. injections in prefilled syringes of (b) (4) In some of the clinical studies, a dose of 150 mg eq. (prefilled syringe, eq. 100 mg/mL) was also evaluated. The injection volume for the paliperidone palmitate formulation increases with increasing dose from 0.25 to 1.5 mL.

Particle size is a main factor driving the release rate of paliperidone palmitate, as already apparent from the early clinical studies (R092670-BEL-1, R092670-BEL-2, R092670-BEL-4). This was later confirmed in Study R092670-PSY-1002, where the PK characteristics of 4 F013 formulations with different particle sizes, including the TBM formulation, were evaluated. In addition, in that study the relative bioavailability compared to an i.m. paliperidone IR formulation was evaluated and the data were used to build an in vitro in vivo correlation model.

Various dosing regimens (double initial dose versus more frequent dosing during the 1st month) were evaluated in Study R092670-BEL-7, in order to identify the dosing regimen that would lead to a rapid attainment of therapeutic plasma concentrations. Initiation of treatment with 2 injections, administered 1 week apart (Day 1 and Day 8), followed by once a month dosing (Day 36 and onwards) was found to result in faster attainment of therapeutic plasma concentrations and of apparent steady state. This dosing regimen was therefore selected and used for all subsequent studies, including Phase 3.

Comparison of the single and multiple dose PK of paliperidone palmitate when injected in the deltoid muscle compared to the gluteal muscle was a main objective in studies R092670-PSY-1004, R092670-USA-3 and R092670-PSY-1001.

In Phase 2 study R092670-SCH-201, the efficacy and safety of paliperidone palmitate was evaluated. In addition, the PK of multiple injections of paliperidone palmitate was compared with that of orally administered paliperidone IR or ER, and the switch from oral paliperidone to i.m. paliperidone palmitate injections was documented.

During the Phase 3 development for paliperidone palmitate, the multiple-dose PK of paliperidone palmitate was documented using plasma concentration data obtained according to a sparse sampling scheme. The short-term (13 week, 4 i.m. injections)

exposure over the dose range of 25 to 150 mg eq. was documented in 2 fixed-dose Phase 3 studies, R092670-PSY-3003 and R092670-PSY-3004. In Study R092670-PSY-3005, initiation of treatment in the deltoid versus the gluteal muscle was compared, the long-term (6 month) exposure was documented, and the switching between deltoid and gluteal injections was evaluated (after 4 i.m. injections). The 1-year exposure of paliperidone palmitate was evaluated in a flexible dose non-inferiority study R092670-PSY-3002, in which steady-state conditions were observed for all doses studied.

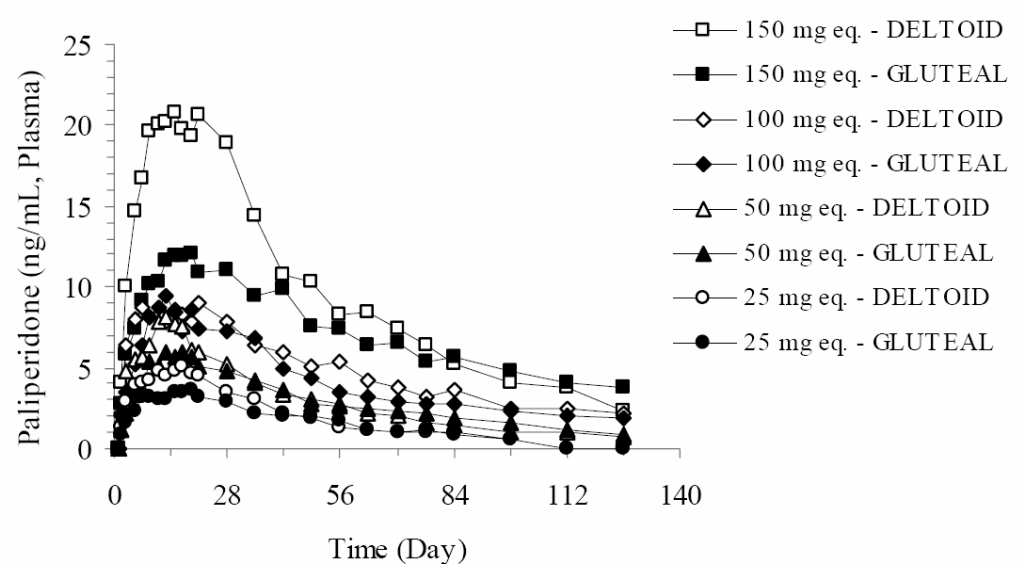
A population PK model to describe the disposition of paliperidone after i.m. injections of paliperidone palmitate, and the impact of various subject covariates on its disposition, was developed. Identification of measurable factors, such as CRCL and BMI, significantly influencing the PK variability provides a more predictive tool for estimating the PK exposure of groups of patients or individual patients, which can be used in evaluations of safety and efficacy and their relationships to drug exposure.

Based on agreements with FDA, results from studies with oral paliperidone ER were used to support the PK of paliperidone after administration of paliperidone palmitate in special populations and the drug-drug interaction potential. No specific studies were performed with paliperidone palmitate.

5. What are the PK characteristics of paliperidone? What are the single dose and multiple dose PK parameters?

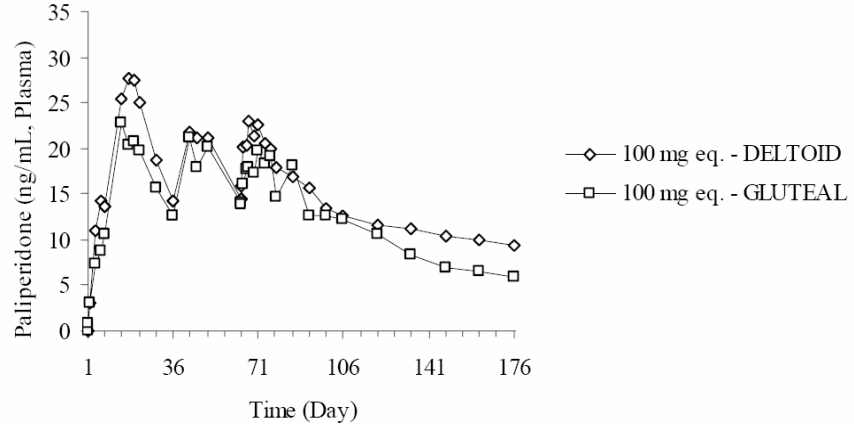
After single dose, PK were compared among different doses between gluteal and deltoid injection in study R092670-PSY-1004.

The total exposure (AUC∞) of paliperidone increased proportionally with dose after single-dose injections of 25 to 150 mg eq. paliperidone palmitate in both the deltoid and gluteal muscle. The increase in Cmax was less than dose proportional for both injections sites at doses greater than 50 mg eq. The Cmax of paliperidone was generally higher after single-dose injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (geometric mean ratio ranging from 108.75% to 164.85%) whereas the difference was less pronounced for AUC∞, (geometric mean ratio ranging from 103.00% to 117.83%). The median apparent half-life was comparable between injection sites. Following figure and table show the median plasma concentration profiles and PK parameters.



	Deltoid											
	25 mg eq.			50 mg eq.			100 mg eq.			150 mg eq.		
PK parameter	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median
t_{max}, days	22	14.69 (9.81)	13.01	23	15.04 (9.63)	13.00	22	17.27 (13.67)	12.51	21	16.58 (10.13)	14.00
C_{max}, ng/mL	22	5.88 (2.31)	5.46	23	10.4 (6.23)	8.79	22	13.4 (7.82)	10.7	21	29.2 (11.8)	27.5
AUC_{last}, ng.h/mL	22	5540 (1831)	5100	19	10033 (4547)	9445	22	16260 (6579)	15484	17	30273 (7625)	28731
AUC_{∞}, ng.h/mL	20	6074 (1942)	5724	18	11800 (4579)	11162	16	20069 (7778)	18675	18	36883 (11095)	33538
$t_{1/2}$, days	20	25.5 (10.2)	24.9	18	33.29 (16.55)	29.06	16	45.7 (16.1)	43.7	18	38.0 (10.6)	40.6
	Gluteal											
	25 mg eq.			50 mg eq.			100 mg eq.			150 mg eq.		
PK parameter	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median	n	Mean (SD)	Median
t_{max}, days	21	19.00 (14.12)	16.00	24	16.70 (10.66)	13.41	25	20.55 (13.25)	14.12	24	23.17 (17.68)	17.03
C_{max}, ng/mL	21	4.89 (2.10)	4.35	24	7.82 (3.28)	6.85	25	12.6 (7.04)	10.7	24	17.9 (9.52)	15.2
AUC_{last}, ng.h/mL	20	4653 (1784)	4771	21	9236 (2417)	8978	21	14520 (7645)	11907	20	23546 (8700)	21984
AUC_{∞}, ng.h/mL	19	5308 (1850)	5435	19	10556 (2039)	10088	18	19674 (8478)	19297	16	30415 (9287)	31344
$t_{1/2}$, days	19	27.1 (15.1)	25.1	19	34.1 (14.3)	31.2	18	40.6 (10.4)	40.0	16	47.5 (19.8)	49.1

In a multiple dose study 1001, the median concentration-time profile of paliperidone, after i.m. administration of 100 mg eq. paliperidone palmitate in the gluteal muscle, was consistently lower compared to i.m. injection in the deltoid muscle as shown in the following figure.

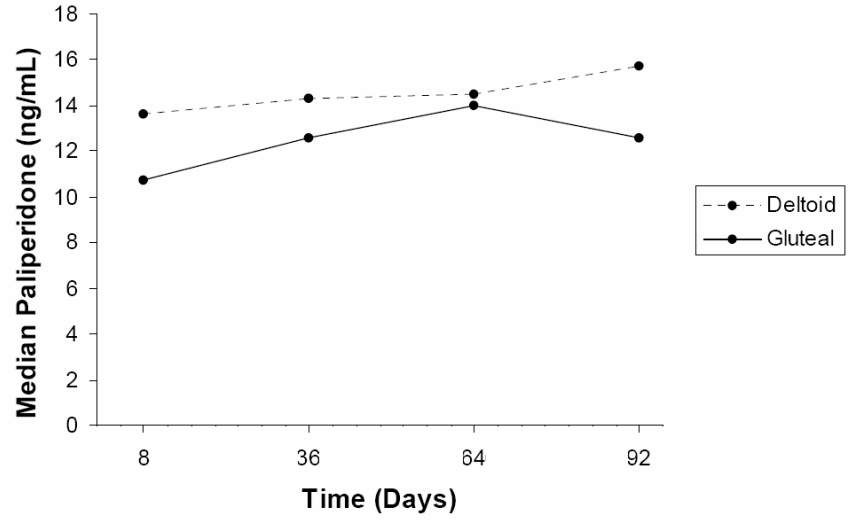


A summary of the PK parameters of paliperidone after i.m administration of 100 mg eq. paliperidone palmitate (on Days 1, 8, 36 and 64), in the deltoid and gluteal muscle is given in the following Table.

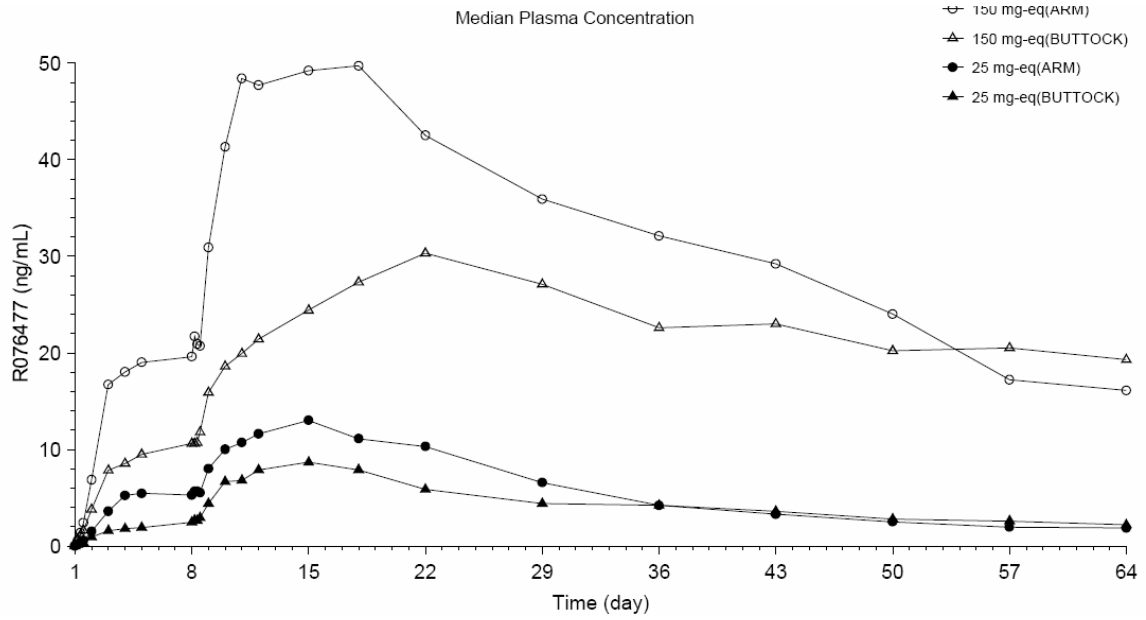
	Second i.m. injection				Fourth i.m. injection			
	Deltoid		Gluteal		Deltoid		Gluteal	
Parameter	n	Median (min - max)	n	Median (min - max)	n	Median (min - max)	n	Median (min - max)
t_{max} (days)	22	9.95 (6.94 – 20.86)	24	10.02 (6.94 – 21.08)	21	4.99 (1.13 – 13.96)	24	6.54 (0.98 – 20.12)
C_{max} (ng/mL)	22	31.3 (15.8 – 67.4)	24	24.1 (9.10 – 50.2)	21	23.7 (8.27 – 71.6)	24	22.3 (6.44 – 56.1)
AUC_{τ} (ng.h/mL)	22	14728 (8253 – 26453)	24	12108 (4736 – 24754)	20	12946 (4287 – 27621)	23	11021 (3198 – 26749)
C_{avg} (ng/mL)	22	21.9 (12.3 – 39.5)	24	18.0 (7.06 – 36.8)	20	19.2 (6.38 – 42.6)	23	16.4 (4.76 – 41.3)
FI (%)	22	88.6 (57.8 – 138)	24	94.8 (53.2 – 160)	20	71.9 (32.6 – 177)	23	56.2 (40.7 – 107)

Note: Paliperidone Palmitate was administered in either the deltoid or gluteal muscle.

The median paliperidone predose plasma concentration on Days 8, 36, and 64 and the plasma concentration on Day 92 are graphically displayed in the following Figure.



In another multiple dose study USA-3, the median plasma concentration-time profiles of paliperidone, after i.m. administration of paliperidone palmitate, were lower for both 25mg and 150 mg eq. dosing groups when injected in the gluteal muscle compared to the deltoid muscle. Paliperidone plasma concentrations reached peak levels for the 25 mg eq. dose group at 10.0 and 6.5 days after gluteal and deltoid injection, respectively. For the 150 mg eq. dose group, tmax was 19 and 11 days after gluteal and deltoid injection, respectively. The obtained median Cmax, after the second dose, for the paliperidone palmitate 25 mg eq. was 10.1 ng/mL for the gluteus and 15.3 ng/mL for the deltoid. For the 150 mg eq. dose group, median Cmax values were 41.0 ng/mL for the gluteus and 66.0 ng/mL for the deltoid. The median plasma exposure after the first and second dose (AUC0-36d) at both dose levels was also lower for i.m. gluteal injections compared to i.m. deltoid injections. The total exposure (AUC∞) was less different between the deltoid and gluteal injections at both dose levels as shown in the following figure.



Pseudo steady state was achieved after the second dose for the 25 mg eq. dose group. This was not the case for the 150 mg eq. dose group, i.e., the median paliperidone plasma concentrations on Day 36, the day of the next i.m. injection if an every-4-hour injection interval would be applied, were higher than those observed on Day 8 (predose to the second injection).

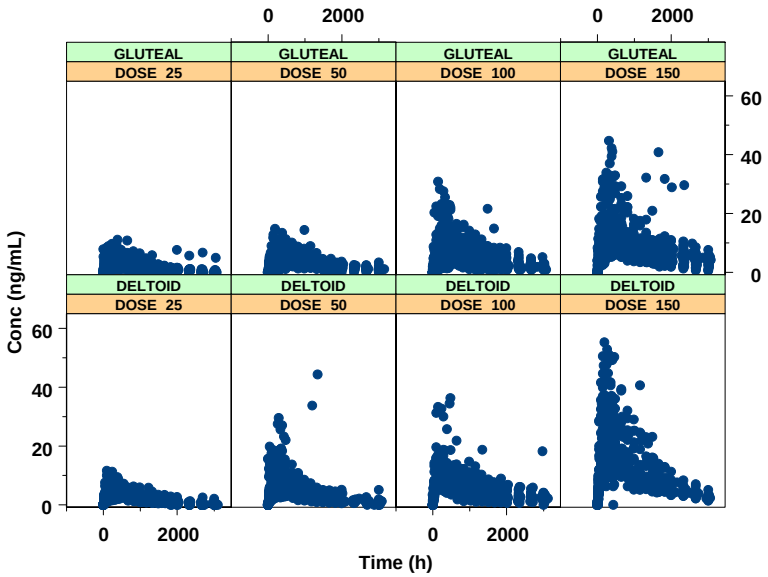
A summary of the pharmacokinetic parameters of paliperidone after i.m. administration of paliperidone palmitate, in the deltoid and gluteal muscle (on Days 1 and 8) is given in Table below. The pharmacokinetic parameters were normalized to 50 mg eq. (2 doses of 25 mg eq.) or 300 mg eq. (2 doses of 150 mg eq.) for the actual dose administered.

Pharmacokinetic Parameter[a]	n	mean ± SD	%CV	median	min - max	n	mean ± SD	%CV	median	min - max
25 mg eq. dose group		Deltoid injection					Gluteal injection			
C_{max2}[b], ng/mL	18	14.8 ± 5.08	34.4	15.3	6.27 - 25.7	21	10.7 ± 5.52	51.7	10.1	2.29 -21.9
t_{max2}[b], days	18	6.36 ± 3.60	56.5	6.05	3.00 - 14.16	21	9.73 ± 8.48	87.2	7.00	2.00 - 35.00
$AUC_{0\text{-}36d}$, ng.h/mL	18	7905 ± 3139	39.7	7709	3686 - 16147	21	5453 ± 2749	50.4	5255	1166 - 11672
AUC_{last}, ng.h/mL	18	10594 ± 4774	45.1	9676	5129 - 24329	21	8151 ± 3864	47.4	7092	1683 - 15560
AUC_{∞}[c], ng.h/mL	15	13116 ± 5602	42.7	11435	6196 - 28311	18	11226 ± 4448	39.6	11040	2447 - 17853
$t_{1/2}$[c], days	15	19.2 ± 6.8	35.4	18.9	8.1 – 30.8	18	28.5 ± 14.8	52.0	23.5	11.6 – 64.6
150 mg eq. dose group		Deltoid injection					Gluteal injection			
C_{max2}[b], ng/mL	19	65.8 ± 24.1	36.6	66.0	33.8 - 119	21	51.4 ± 30.0	58.4	41.0	19.9 - 117
t_{max2}[b], days	19	10.70 ± 8.07	75.4	10.00	0.00 - 28.00	21	18.85 ± 17.42	92.4	10.00	2.01 - 56.00
$AUC_{0\text{-}36d}$, ng.h/mL	19	34456 ± 12680	36.8	32444	17127 - 57605	22	24071 ± 13346	55.4	21007	8627 - 62040
AUC_{last}, ng.h/mL	18	50951 ± 19638	38.5	48102	22447 - 90945	21	41144 ± 15589	37.9	38099	13962 - 76629
AUC_{∞}[c], ng.h/mL	17	67061 ± 26518	39.5	63249	24548 - 112073	13	61437 ± 17656	28.7	54659	36733 - 91019
$t_{1/2}$[c], days	17	26.4 ± 8.9	33.6	23.5	13.7 – 43.3	13	29.0 ± 10.1	34.8	27.1	12.2 – 48.8

[a] Pharmacokinetic parameters were corrected for the actual dose administered and normalized to 2 times 25 or 2 times 150 mg eq., respectively.
[b] An i.m. dose was administered on Days 1 and 8, after which the pharmacokinetic profiles were determined. The time at which the maximum concentration (C_{max2}) is achieved after the second dose is reflected in t_{max2}.
[c] Interpret with caution because for some subjects $\%AUC_{ex}$ was higher than 20%.
Acronym: CV: coefficient of variance.

6. What is the degree of linearity or nonlinearity in the dose-concentration relationship for paliperidone?

The following figure shows the concentration profiles for different doses and injection sites in study 1004.



From the graph, it seems that the concentration increases when the dose increases. The sponsor concluded that the dose proportionality had been established for AUC. To confirm the sponsor's conclusion, the reviewer conducted a dose proportionality analysis using a power model shown below.

$Par = a \times (Dose)^b$

where Par stands for the parameters, such as AUC and Cmax; Dose is the paliperidone dose; a and b are constants. If b is near 1 (the confidence limit including 1), then the linearity is indicated. Log transformation was performed on the above formula, resulting in the following formula.

$\log(Par) = \log(a) + b \times \log(Dose)$

The following table shows the results from SAS procedure glm (generalized linear model).

Parameters	Log(a)	b		
		Estimate	95% confidence interval	90% confidence interval
AUC	5.526	0.898	0.772-1.023	0.792-1.003
Cmax	-0.7758	0.748	0.626-0.871	0.646-0.851

Although AUC barely meets the criteria, Cmax is out of the range. Therefore, the dose proportionality for Cmax is not established.

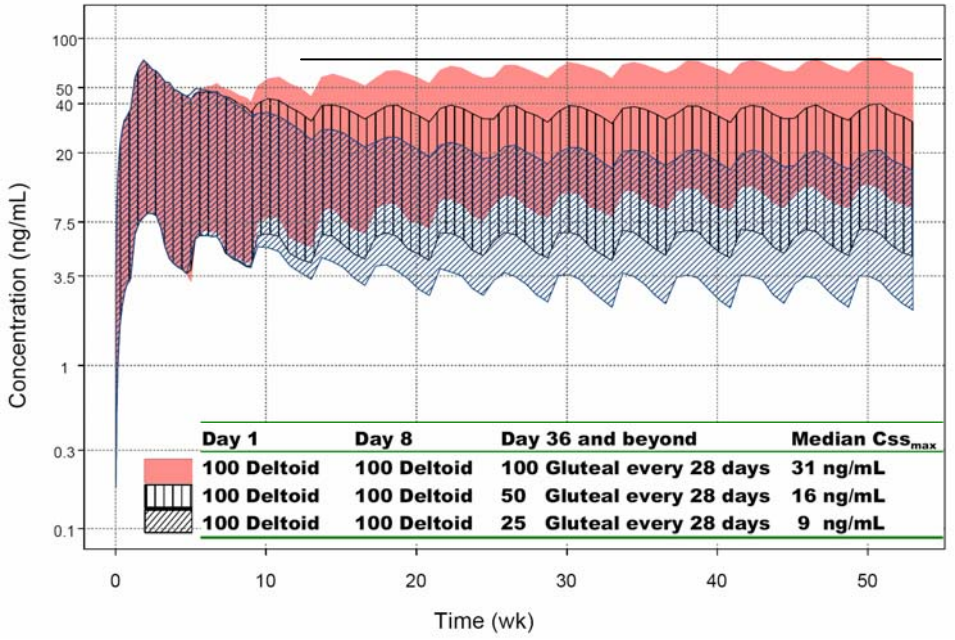
7. Is the proposed dosing regimen adequate?

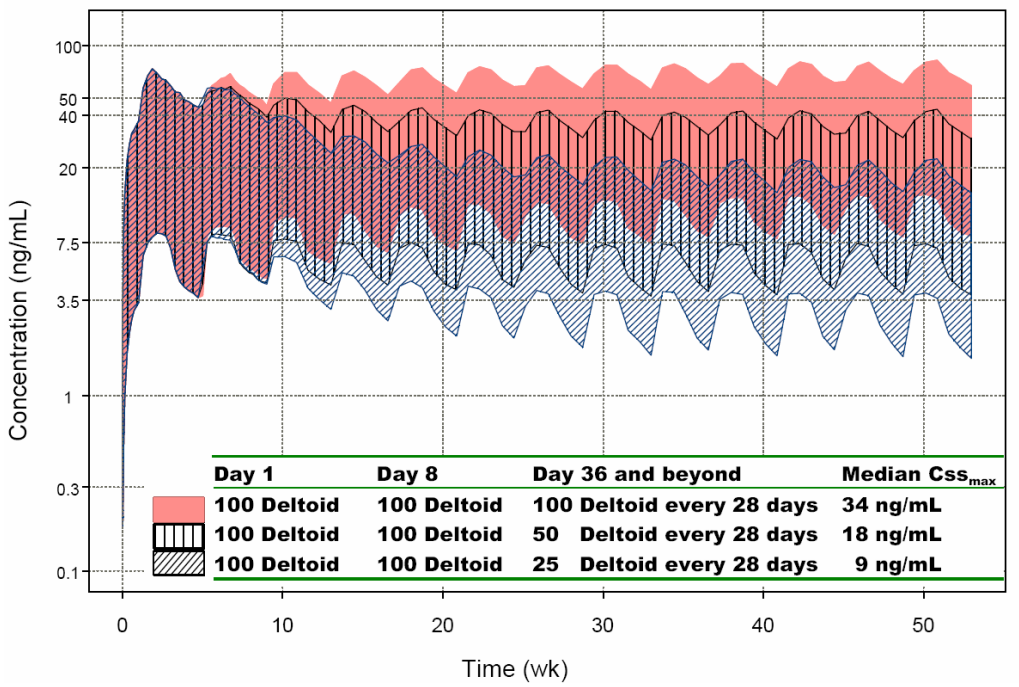
The proposed paliperidone palmitate dosing is monthly (every 4 weeks) injections of 25 to 100 mg eq. (deltoid or gluteal intramuscular administration) after 2 initial doses of (b) (4) mg eq. (deltoid administration) on Days 1 and 8. For deltoid administration, a 1.5-inch needle should be used for patients >=90 kg and a 1-inch needle for patients <90 kg.

The 100 mg eq. injection in the gluteal muscle has been used in Phase 3 trials but the proposed initiation dosing regimen as described above has not been studied in Phase 3 trials.

The applicant performed various simulations of PK profiles to support the proposed initiation of treatment with 100 mg eq. deltoid doses so to achieve potential therapeutic concentrations more quickly.

Simulation of initiation doses (different from those studied in Phase 3 trials) were performed with 100 mg eq. deltoid injection on day 1 and 8 followed by monthly injections of 25, 50 or 100 mg eq. in either the deltoid or gluteal muscle. The results of these simulations are presented in the following Figures. The upper panel depicts the impact of switching injection-sites on day 36, while the lower panel shows the impact on PK when the deltoid site is also used for maintenance injections on day 36 and beyond. The two time-windows of primary interest in the upper panel and the lower panel are the early period of initiation and the profile at steady-state at one year. The initial two deltoid injections of 100 mg eq. help attain potential therapeutic concentrations rapidly with exposures that were similar to the maximum steady-state level achieved at one year with the 100 mg eq. gluteal injections.



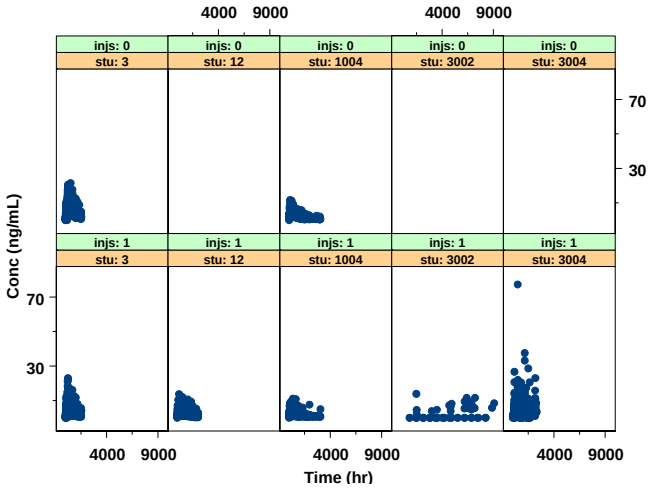


Thus, based on the PK profiles, the applicant considered initiation dosing regimen proposed [redacted] (b) (4) eq. in the deltoid muscle on days 1 and 8) a safe and convenient method of more rapidly achieving potential therapeutic concentrations compared to initial injections into the gluteal muscle. Furthermore, even if the injection site is not changed to the gluteal muscle after the second dose, the concentrations at steady-state from the deltoid injection will not be substantially higher than from gluteal injections. The median peak at steady-state for repeated gluteal and deltoid injections (administered on day 36 and beyond) were 31 and 34 ng/mL.

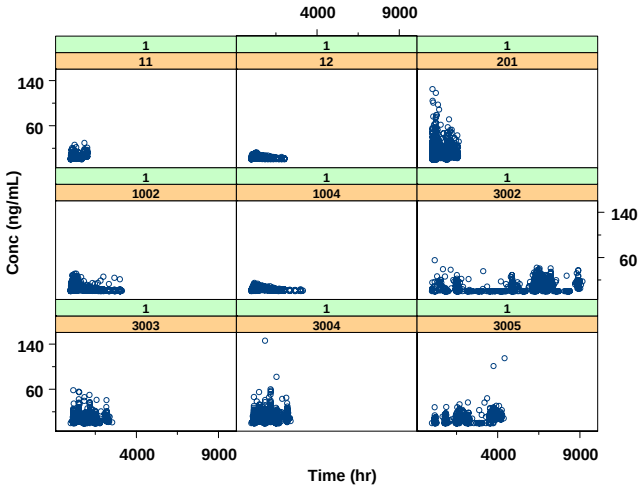
To evaluate the adequacy of this proposed initial dosing regimen, several aspects are considered.

First of all, the concentrations are compared across studies at different doses for different injection sites. In the following figures, there are two panel strips to differentiate the injection sites and studies. The upper one shows the injection sites: 0 for deltoid and 1 for gluteus; the lower strip indicates the study number.

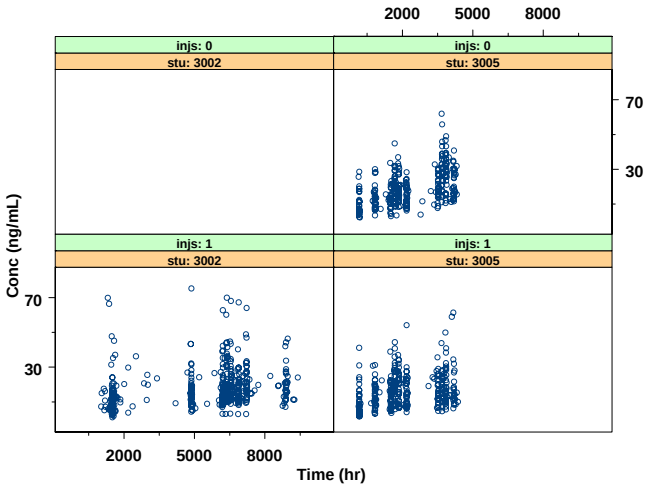
Figure below demonstrates the concentration profiles for different injection sites at dose of 25 mg. The concentrations of Phase 3 study 3004 seem to have a wider range.



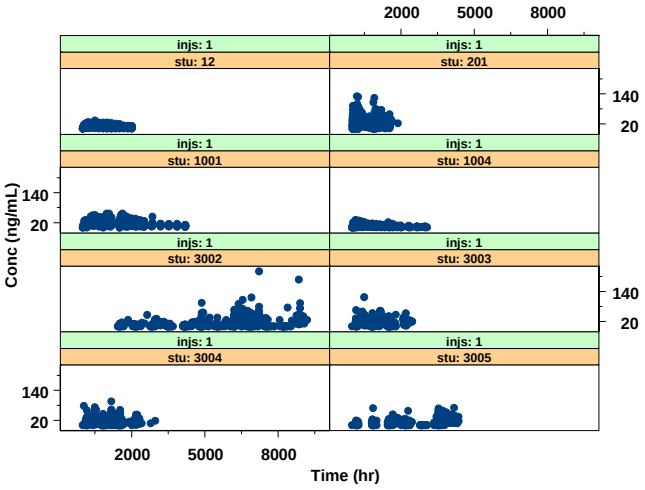
Following figure shows the profile for gluteal injection site at dose of 50 mg. The concentrations in phase 2/3 studies 201, 3003, 3004, and 3005 have wider ranges compare to Phase 1 studies (11, 12, 1002, and 1004).



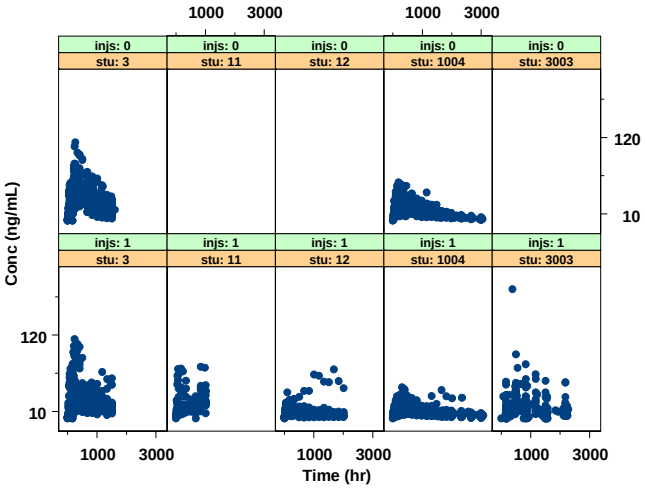
Following figure shows the profile for different injection sites at dose of 75 mg.



Following figure shows the profile for dose of 100 mg at gluteal injection site. Phase 2/3 studies seem to have wider concentration ranges compared to Phase 1 studies.



Following figure shows the profile for different injection sites for dose of 150 mg.

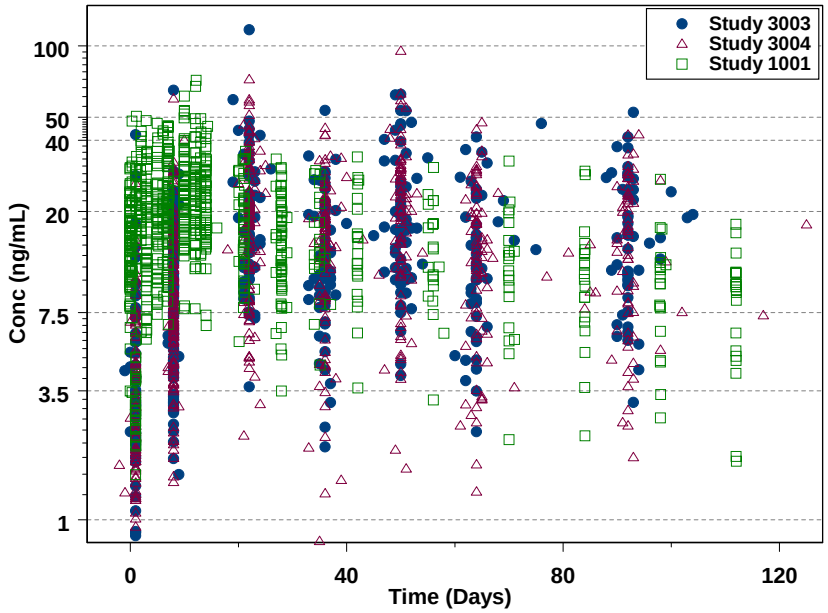


From above figures, two inferences can be made.

1. The concentrations obtained from deltoid injection are higher than those from gluteal injection.
2. The concentrations in Phase 2/3 studies are generally in a wider range due to the fact that the phase 1 studies had more strict selection criteria compared to phase 2/3 studies. Therefore, from the efficacy and safety perspectives, the concentrations in Phase 2/3 studies should be used as references for considerations.

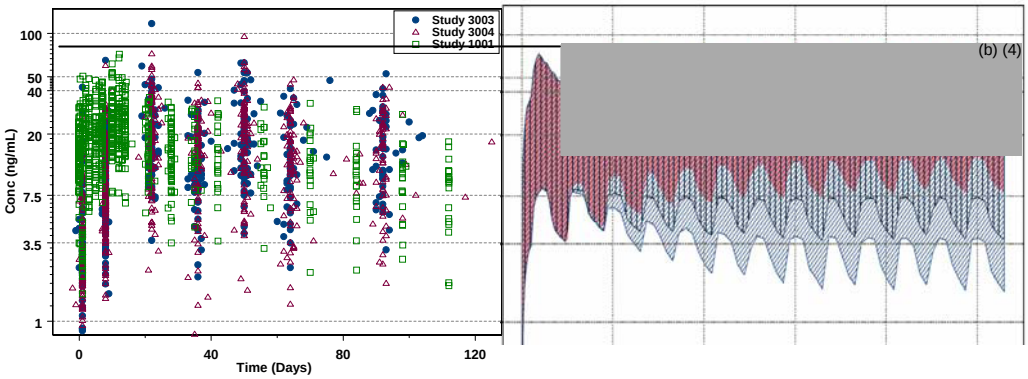
Based on the results of the paliperidone ER tablets Phase 3 studies, in which plasma samples were collected at several time points after administration of the recommended 6 mg dose, a plasma concentration of 7.5 ng/mL was identified as the effect concentration above which 90% of the plasma concentrations were observed (paliperidone ER tablets Studies: R076477-SCH-303/-304/-305). This value of 7.5 ng/mL was used by the applicant to assess the initiation-dosing regimen with the first two doses of 100 mg eq. in the deltoid muscle for paliperidone palmitate. Simulations with the proposed regimen

indicated that at 1 wk after the first dose, majority of the subjects (more than 73%) obtain plasma concentrations above 7.5 ng/mL. Thus, the applicant concluded that the proposed initiation regimen might represent a viable method for attaining potential therapeutic concentrations rapidly. However, considerable samples of the acutral concentrations achieved in phase 3 studies were lower than this level. Following figure shows the concentrations in studies 3003, 3004, and 1001 where 100 mg eq. dose was used.



As shown in the above figure, the concentrations in studies 3003 and 3004 were frequently below the line of 7.5 ng/mL. This indicates that the lower limit set for the simulation based on the oral tablets formulation might be high enough.

On the other hand, the upper limit of the concentration is a safety concern. To address this issue, the actual data from the above figure and the results of simulation are compared by putting them side by side as shown in the following figure. Note that the left panel is from above figure with 100 mg eq, dose. Only the pink shaded area should be considered in the right panel. The pink shaded area, representing 90% prediction interval, is for the scenario in which 100 mg eq. deltoid injection on day 1 and 8 followed by monthly injections of 100 mg eq. in the deltoid. It is the highest exposure for the proposed dosing regimens.



Quantitatively speaking, the median Cmax is 23.7 to 31.3 ng/mL in study 1001 while the simulated median Css,max is 34 ng/mL. These values are compared to the exposures in multiple dose oral ER tablets of paliperidone. Following table shows the PK parameters of paliperidone ER tablets measured at Day 6 after dose of 12 mg qd (n=34).

Cpredose, (ng/ml)	Cmin, (ng/ml)	Cmax, (ng/ml)	Tmax, (h)	AUCτ (ng.ml x hr^{-1})	Cavg,ss (ng/ml)	CL/F (ml/min)
41.5 ± 22.4 (54.0) 15.9 - 135 [36.0]	31.4 ± 15.9 (50.6) 13.2 - 92.4 [28.6]	45.6 ± 27.1 (59.4) 16.6 - 166 [38.4]	14.7 ± 10.1 (68.7) 0.9 - 24.0 [22 2]	896 ± 507 (56.6) 359 - 3126 [769]	37.3 ± 21.1 (56.6) 15.0 - 130 [32.1]	273 ± 113 (41.4) 64.0 - 557 [260]

Following table shows the PK parameters of paliperidone ER tablets measured at Day 14 after dose of 9 mg qd (n=32).

Cmin,ss ng/mL	Cmax,ss ng/mL	tmax,ss h	AUCτ,ss, ng.h/mL	Cavg,ss, ng/mL	Cmax,ss: Cmin,ss Ratio	CL/F mL/min
25.3 ± 16.2 (63.8) 3.86 - 76.9 [21.7]	40.2 ± 24.1 (59.9) 8.79 - 130 [35.0]	10.90 ± 8.88 (81.4) 1.87 - 24.00 [8.99]	762 ± 464 (60.9) 173 - 2331 [638]	31.7 ± 19.3 (60.9) 7.19 - 97.1 [26.6]	1.69 ± 0.49 (28.8) 1.15 – 3.07 [1.6]	274 ± 169 (61.6) 64.4 - 869 [235]

The recommended dose for paliperidone ER tablets is 6 mg QD with maximum dose of 12 mg. The currently proposed initial dosing regimen may generate exposures comparable to that of 7.5 mg ER tablets QD dosing, which is higher than the 6 mg QD dosing. However, it is lower than that of the maximum recommended oral ER tablets 12 mg QD dosing.

Based on study 1001, the PK parameters after the second deltoid injection 100 mg eq. are shown below.

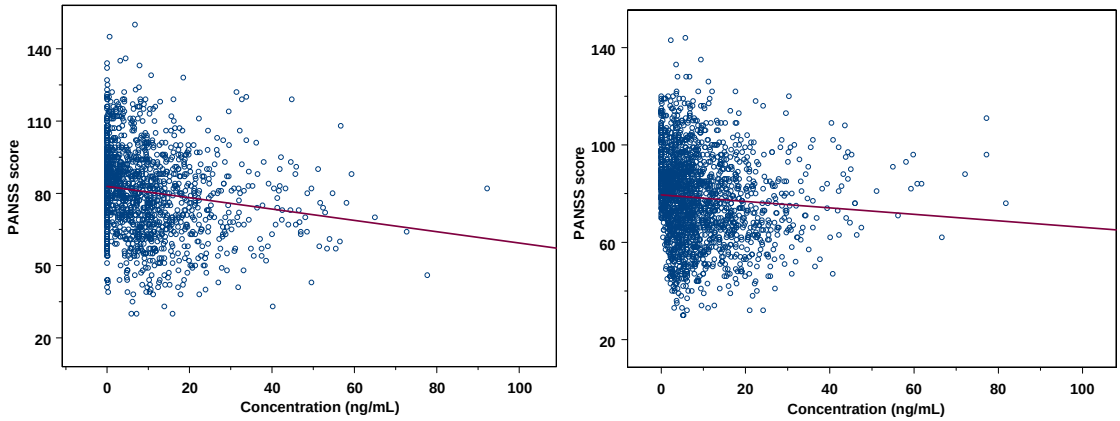
N	Cmax,ss ng/mL	tmax h	AUCτ* ng·h/mL	Cavg ng/mL	FI (%)
22	31.3 (15.8-67.4)	9.95 (6.94-20.86)	14728 (8253-26453)	21.9 (12.3-39.5)	88.6 (57.8-138)

* AUC during 28 days, convert to AUC24h=526 ng·h/mL

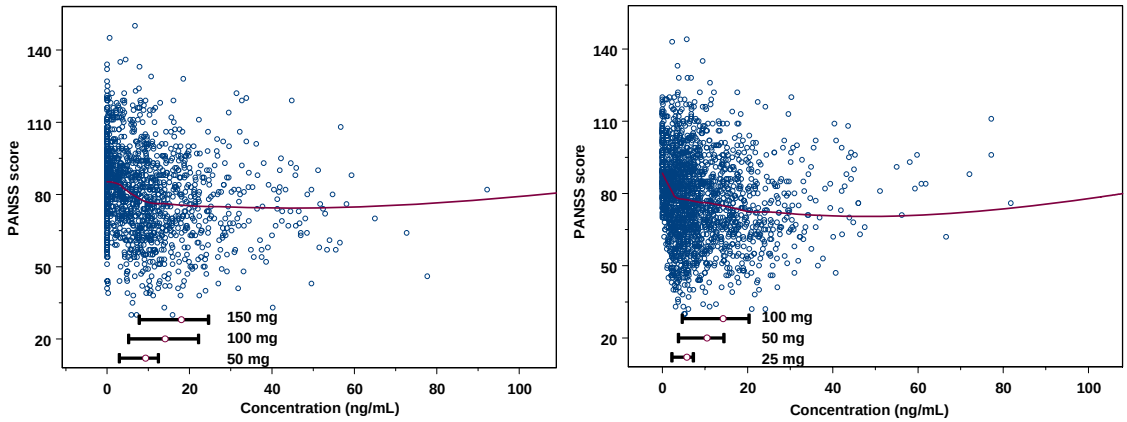
Compared to the exposure oral ER paliperidone dose of 6 mg (Cmax 23.3 ng/mL, AUC24h 425 ng·h/mL, median values obtained from 9 mg data assuming linear kinetics), the exposure of proposed initial dosing regimen is 24-34% higher. Therefore, the 75 mg eq. initial deltoid injection seems more appropriate.

Secondly, the time course of the efficacy (PANSS score) is examined.

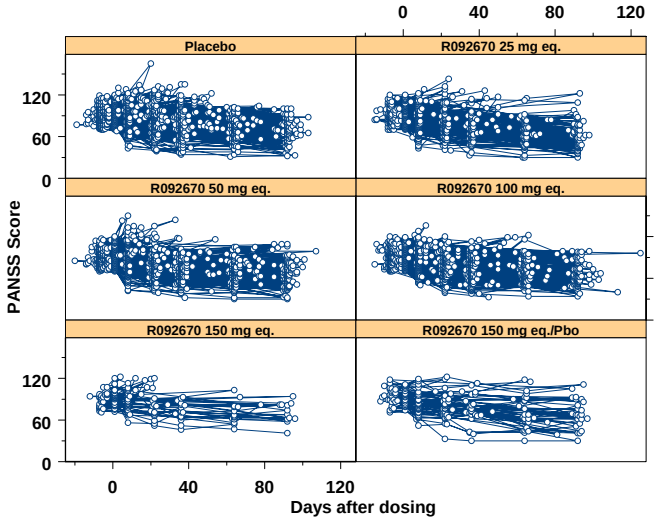
Study 3003 and 3004 were fixed dose studies. The following figure shows the relationship between concentrations and PANSS scores in study 3003 (left panel) and study 3004 (right panel). It appears that the PANSS scores decrease when concentrations increase. Linear regression shows a significant relationship with $p<0.0001$.



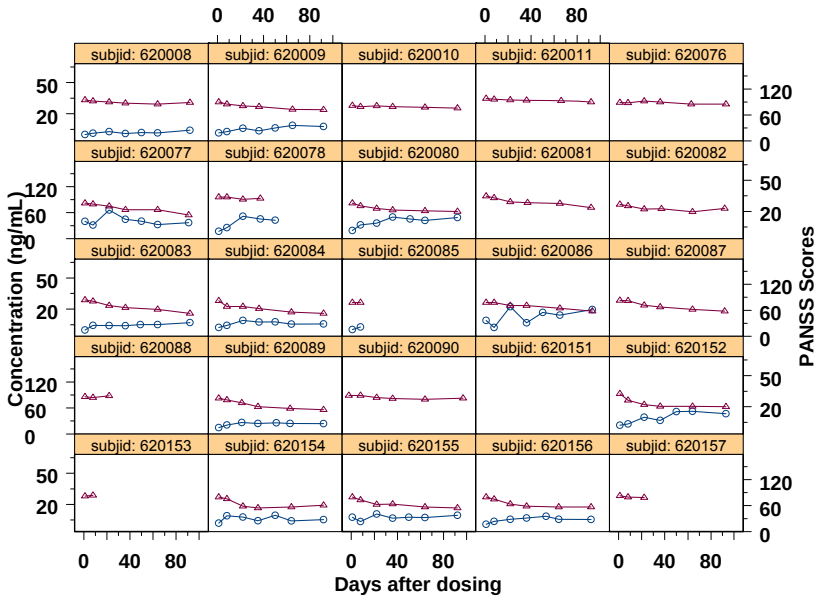
However, the loess regression is more appropriate for the relationship between PANSS and concentraions as shown in the following figures. They indicate that when the concentrations increase initially PANSS scores decrease considerably, while as the concentrations increase further, the PANSS scores do not change much (left panel for study 3003 and right for 3004).



The following plots show the longitudinal plots using combined PANSS scores data from studies 3003 and 3004.



As seen, the PANSS scores dropped initially, and were relatively flat after the initial drops. If looking at the PANSS scores at individual level from randomly selected subjects of study 3003, this observation can be confirmed as shown in the following figures (the concentrations are plotted as blue circles and the PANSS scores are plotted as red triangles).



From these observations, the initial concentrations seem to be important for the efficacy. On the other hand, the concentrations are related to the occurrences of the adverse events.

Therefore, considering the importance of initial exposure, initial deltoid injection may be beneficial for quicker achieving desired efficacy. However, compared to the exposure achieved by oral ER paliperidone at recommended dose of 6 mg (Cmax 23.3 ng/mL, AUC24h 425 ng·h/mL, median values obtained from 9 mg data assuming linear kinetics), the exposure of proposed initial dosing regimen is 24-34% higher. Therefore, the 75 mg eq. initial deltoid injection is recommended for the initial dosing regimen.

8. What are the effects of injection sites?

Injection of paliperidone palmitate in the deltoid or the gluteal muscle has been compared in three Phase 1 clinical trials with extensive PK sampling (R092670-USA-3, R092670-PSY-1001, and R092670-PSY-1004) and in one Phase 3 trial with sparse sampling (R092670-PSY-3005).

A summary of the comparison of the geometric mean exposure parameters (Cmax and AUC∞) of paliperidone in single dose study 1004 for each dose after deltoid injection compared to gluteal injection of paliperidone palmitate (ratio deltoid/gluteal), is shown in Table below. The geometric mean Cmax was higher after deltoid injection compared to gluteal injection for all doses.

Dose	Parameter	Ratio, % (Deltoid/Gluteal)	90% CI (Original Scale)
25 mg eq.	AUC_{∞} (ng.h/mL)	117.83	(96.63 ; 143.69)
	C_{max} (ng/mL)	119.85	(96.20 ; 149.30)
50 mg eq.	AUC_{∞} (ng.h/mL)	104.38	(88.38 ; 123.27)
	C_{max} (ng/mL)	119.91	(93.41 ; 153.92)
100 mg eq.	AUC_{∞} (ng.h/mL)	103.00	(79.02 ; 134.26)
	C_{max} (ng/mL)	108.75	(84.61 ; 139.78)
150 mg eq.	AUC_{∞} (ng.h/mL)	114.43	(97.64 ; 134.11)
	C_{max} (ng/mL)	164.85	(131.21; 207.12)

Data analyzed on log-scale and results transformed back to the original scale

For multiple dose study 1001, a summary of the comparison of the geometric mean exposure parameters (Cmax and AUCt) of paliperidone after the fourth i.m. injection between deltoid and gluteal, performed on log-transformed data, is shown in the following Table.

Parameter	Estimated Ratio (%)[a] (Deltoid (n=19)/Gluteal (n=23))	90% CI
AUC_{τ} (ng.h/mL)	120.00	(93.09-154.69)
C_{max} (ng/mL)	130.34	(100.56-168.93)

[a] Data analyzed on log scale, but statistics transformed back to original scale .
CI: Confidence interval

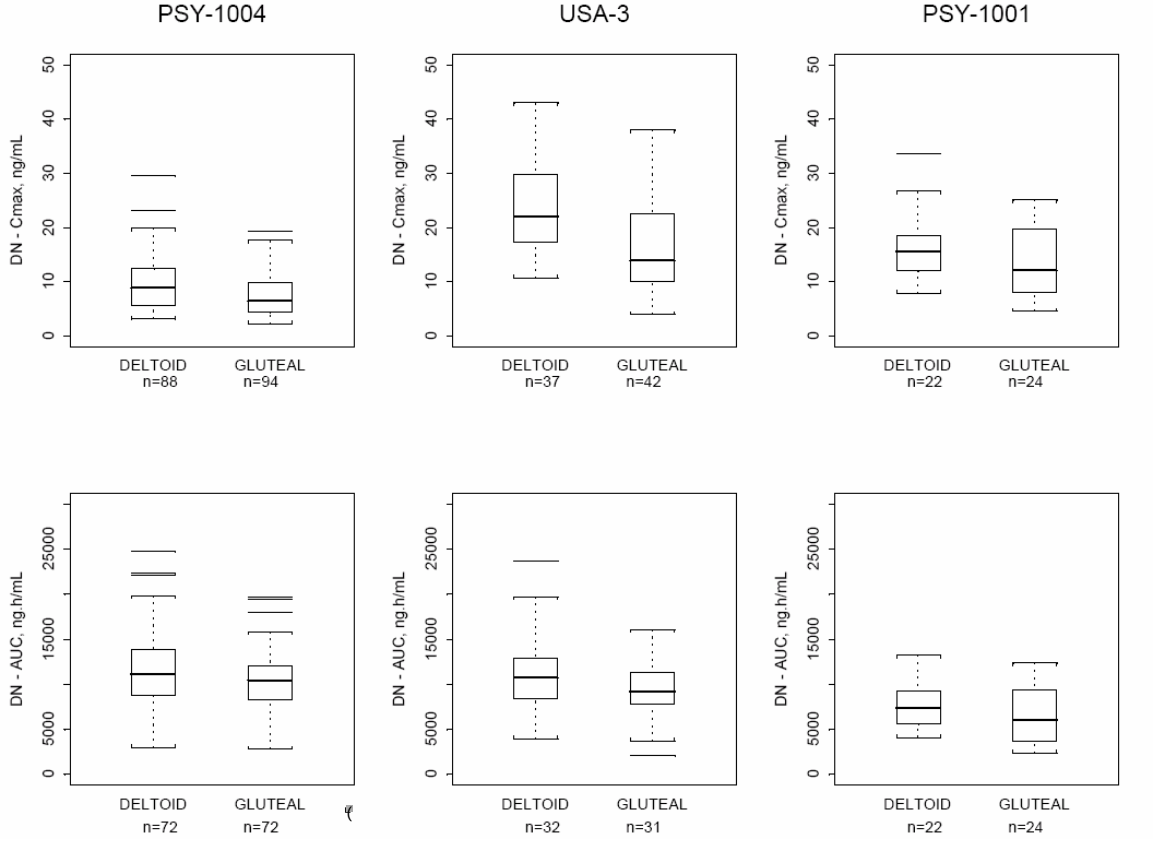
In another multiple dose study USA-03, the treatment ratios of the dose adjusted AUC0-36d, AUC∞, AUClast, and Cmax2 did not fall within the equivalence range of 80-125%. The peak and AUC0-36d (relative bioavailability) was approximately 50% higher after injection in the deltoid compared to gluteal muscle. However, for the total estimated exposure, AUC∞, the difference is less between both injection sites as shown in the following table.

Pharmacokinetic Parameter[a,b]	Dose	Least square means				A/B, %	
		n	Deltoid (A)	n	Gluteal (B)	Ratio	90% CI
AUC_{0-36d}, ng.h/mL	25 mg eq.	18	7350	21	4788	153.53	(118.13; 199.54)
	150 mg eq.	19	32215	22	21219	151.82	(119.52; 192.85)
AUC_{∞}, ng.h/mL	25 mg eq.	15	12227	18	10139	120.60	(91.97; 158.14)
	150 mg eq.	17	61670	13	59142	104.27	(82.05; 132.52)
AUC_{last}, ng.h/mL	25 mg eq.	18	9755	21	7224	135.03	(104.01; 175.31)
	150 mg eq.	18	47195	21	38299	123.23	(98.85; 153.61)
C_{max2}, ng/mL	25 mg eq.	18	13.9	21	9.28	149.69	(114.87; 195.05)
	150 mg eq.	19	61.9	21	44.3	139.74	(108.75; 179.56)

[a] Data analyzed on log scale and statistics transformed back to original scale.
[b] Pharmacokinetic parameters were corrected for the actual dose administered and normalized to 2*25 or 2*150 mg eq.

In these Phase 1 studies, at the initiation of treatment, injection of paliperidone palmitate in the deltoid muscle consistently resulted in higher plasma concentrations compared to injections in the gluteal muscle. Also, the observed Cmax was higher after injection in the deltoid muscle compared to the gluteal muscle in all Phase 1 studies where gluteal and

deltoid injections were compared. As shown in the following figures, the dose normalized Cmax and AUC are higher for deltoid injection than that for gluteal injection.



For the proposed dosing regimen of an i.m. injection of paliperidone palmitate (b) (4) eq. on Day 1 and Day 8, the ratio of geometric mean Cmax (deltoid/gluteal) after the second injection on Day 8 (dosing interval Day 8 to Day 36) was estimated to be 129.16%. In line with this, in Study R092670-USA-3, the difference in Cmax after the second injection on Day 8 between deltoid and gluteal injections was estimated to be 149.69% for the 25 mg eq. and 139.74% for the 150 mg eq. dose. These observations are also in line with the estimated difference in Cmax, irrespective of dose (25 to 150 mg eq.), of 127.86% after a single injection in the deltoid vs. the gluteal muscle. After the fourth injection of 100 mg eq. paliperidone palmitate on Day 64 (R092670-PSY-1001), the median Cmax was 22.3 ng/mL in the gluteal vs. 23.7 ng/mL in the deltoid muscle, most likely as plasma concentrations were approaching steady state at that time.

In all the Phase 1 studies, a difference between injection sites was less pronounced for AUC than for Cmax, indicating that the overall exposure to paliperidone is less different between the two injection sites after i.m. administration of paliperidone palmitate.

A difference between injection in the deltoid or the gluteal muscle can likely be explained by the different distribution of muscle and adipose tissue between the 2 injection sites, which may affect the dissolution of paliperidone palmitate and the subsequent uptake of paliperidone by the circulation at the site of injection. At the deltoid injection site, the likelihood of an injection that is purely intramuscular is higher compared to the gluteal

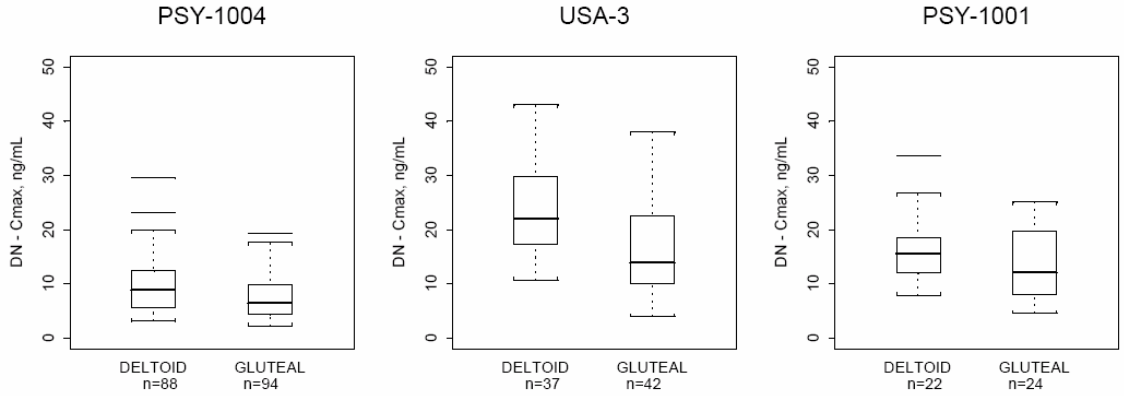
injection site. The hypovascularity of subcutaneous adipose tissue compared with muscle tissue may result in a slower uptake of paliperidone from the gluteal compared to the deltoid injection site, due to the slower dissolution of the palmitate at the gluteal injection site. The latter has been shown for injectable lidocaine, for which a delayed release/onset of action in subjects with a high BMI was observed. This effect will have a greater impact at the initiation of treatment. After multiple injections, fluctuations in paliperidone plasma concentrations are reduced since steady state is approached, and a difference between deltoid and gluteal injections will be less apparent.

The effects of the injection site are also supported by the population PK analysis. Injection site was identified as a covariate for the fraction (F2) of the dose that is released from the injection site through an initial relatively fast zero-order process. It was shown that injection in the deltoid muscle resulted in a 37% higher F2 compared to injection in the gluteal muscle, leading to higher paliperidone plasma concentrations at initiation of treatment with paliperidone palmitate.

9. What are the effects of needle length?

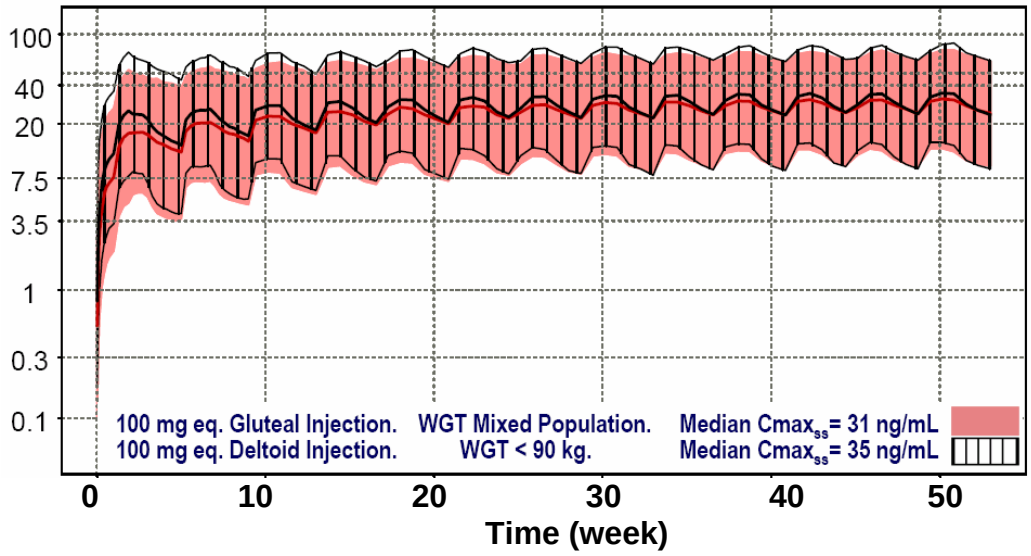
An important factor affecting the proper administration of paliperidone palmitate in order to achieve injection in the musculature (as opposed to adipose tissue) and optimal paliperidone exposure, in particular in subjects with a high BMI (body weight), is the needle length used for injection of paliperidone palmitate in the gluteal or the deltoid muscle.

Needle length is related to plasma concentration. In Study R092670-USA-3, a 1.5-inch needle was used for gluteal and deltoid injections, while in studies R092670-PSY-1004 and R092670-PSY-1001, a 1.5-inch needle was used for gluteal injections while a 1-inch needle was used for deltoid injections, regardless of body weight. When comparing the results of these studies, it can be seen that the difference in Cmax between injections in the deltoid vs. the gluteal muscle was larger when a 1.5-inch needle was used for the deltoid muscle, compared to injections with a 1-inch needle as shown in the following figure for dose normalized Cmax values in different studies.

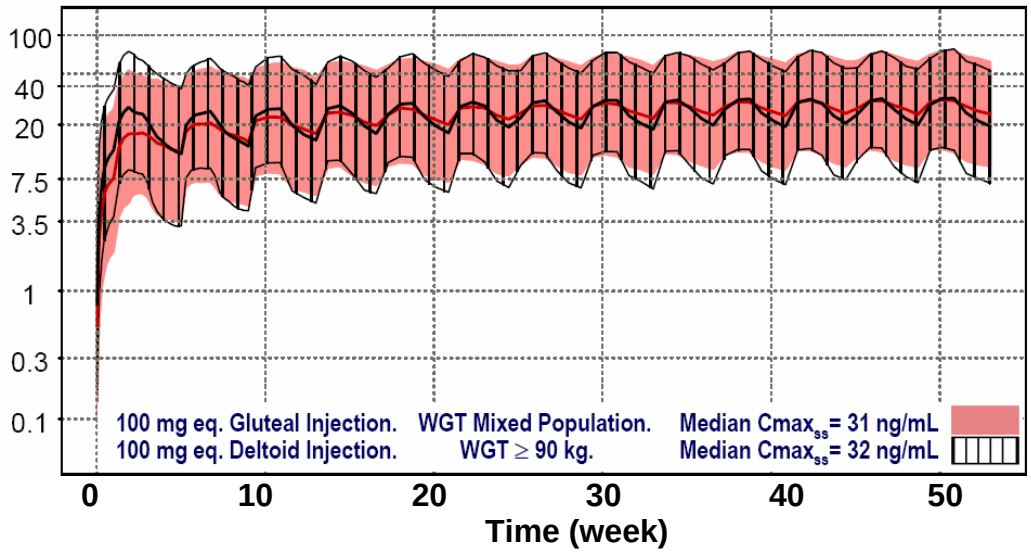


This may be explained by the fact that for some subjects, based on their body weight and BMI, the use of a 1.5-inch needle for the deltoid injections is more likely to result in a 'true' i.m. injection compared to a 1-inch needle.

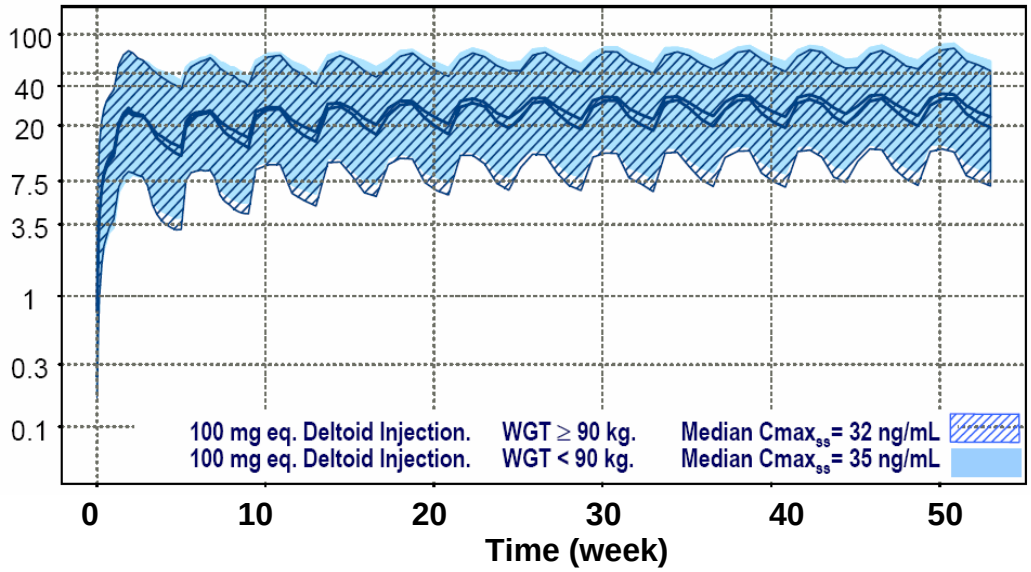
The impact of needle length was explored using population PK simulations, as needle length was used as a covariate in the population PK model. Comparison of the gluteal and deltoid injections using 2 needle lengths showed that deltoid injections will provide higher initial concentrations resulting in a more rapid attainment of potential therapeutic plasma concentrations. However, comparing gluteal vs. deltoid injections using a 1-inch needle in individuals <90 kg predicts a slightly higher peak and slightly lower trough concentration at steady-state for the deltoid vs. the gluteal injection (median peak: 35 vs. 31 ng/mL and median trough: 23 vs. 24 ng/mL) as shown in the following figure. These differences are considered to be of no clinical relevance. In the following figures, the shaded areas and lines represent the 90% prediction interval and the median. Displays use a logarithmic concentration scale. Simulations were performed with the needle length as with deltoid injections, subjects with weight (WGT) >=90 kg were injected using a 1.5-inch needle and subjects with WGT< 90 kg were injected using a 1-inch needle. For gluteal injections only 1.5-inch needle was utilized.



For heavier individuals (weight >=90 kg), injections in the deltoid muscle with a 1.5-inch needle would yield a steady-state maximum plasma concentration that was similar to gluteal injections (median: 32 vs. 31 ng/mL) as shown in the following figure. Thus, it appears that in heavier subjects, the deltoid injection behaves like the gluteal administration provided a 1.5-inch needle was used. This was expected because heavier individuals may have more extensive adipose tissue deposition in the deltoid muscle region.



Deltoid injection was also compared between the 2 weight groups with different needle lengths. It shows that using the longer needle in the deltoid muscle for the =90 kg group would eliminate the body size influence. The longer needle used for injection in the deltoid for heavier individuals thus yielded a profile that was super-imposable on the concentration-time profiles from the lower-weight group that used the shorter needle as shown in the following figure.



10. What formulations were used in the clinical studies?

The applicant intends to market paliperidone palmitate aqueous suspension (eq. 100 mg/mL) for i.m. injection in prefilled syringes of 25, 50, 75, and 100 mg eq. All dose strengths are proportional in composition. The following table shows the formulations used in different clinical studies.

Formulation Number	Batch Number	Particle Size[a] (d_v50, µm)	Volume[b]	Clinical Study (R092670-)[c]
To-be-marketed (TBM) Formulation				
F013	05C24/F013	(b) (4)	0.25 mL	PSY-1004[f], PSY-3001, PSY-3002, PSY-3003, PSY-3004
			0.5 mL	PSY-1004[f], PSY-3001, PSY-3002, PSY-3003, PSY-3004, PSY-3005[f]
			0.75 mL	PSY-3005[f]
			1 mL	PSY-1001[f], PSY-1004[f], PSY-3001, PSY-3002, PSY-3003, PSY-3004, PSY-3005[f]
			1.5 mL	PSY-1004[f], PSY-3003
	05E12/F013A		0.25 mL	PSY-3001, PSY-3002, PALM-JPN-1
	05E12/F013B		0.5 mL	PSY-3001, PSY-3002, PSY-3003, PSY-3004, PSY-3005[f]
	05E12/F013C		0.75 mL	PSY-3001, PSY-3002
	05E12/F013D		1 mL	PSY-3001, PSY-3002
	05E26/F013C		0.5 mL	PSY-1002
	05I07/F013A		0.25 mL	PSY-3001
	05I07/F013B		0.5 mL	PSY-3001, PSY-3002, PSY-3003, PSY-3005[f], PALM-JPN-1
	05I07/F013C		0.75 mL	PSY-3002, PSY-3005[f]
	05I07/F013D		1 mL	PSY-3001
	05I07/F013E		1.5 mL	PALM-JPN-1
	05J19/F013A		0.25 mL	PSY-3001, PSY-3002
	05J19/F013B		0.5 mL	PSY-3001, PSY-3002
	05J19/F013C		0.75 mL	PSY-3001, PSY-3002
	05J19/F013D		1 mL	PSY-3001, PSY-3002
	06A24/F013A		0.25 mL	PSY-3001, PSY-3002
	06A24/F013B		0.5 mL	PSY-3001, PSY-3002
	06A24/F013C		0.75 mL	PSY-3001, PSY-3002
	06A24/F013D		1 mL	PSY-3001, PSY-3002
	06D10/F013B		0.5 mL	PSY-3001
	06D10/F013C		0.75 mL	PSY-3001
	06D10/F013D		1 mL	PSY-3001
	F013 formulations with broader particle size ranges used for IVIVC, not intended for marketing			
	05E26/F013A[d]	(b) (4)	0.5 mL	PSY-1002
	05E26/F013B[d]		0.5 mL	PSY-1002
	05E26/F013D[d]		0.5 mL	PSY-1002
F011 Formulation				
F011* (Phase 1/2)	01C16/F011[e]	(b) (4)	1.5 mL in vial	INT-11[g], INT-12[g], SCH-201[g]
	01D06/F011[e]		1.5 mL in vial	USA-3[g], SCH-201[g]
F011 (Phase 3)	04D13/F011		0.25 mL	PSY-3001, PSY-3002, PSY-3004
			1 mL	PSY-3002, PSY-3004
	04E05/F011		0.25 mL	PSY-3004
			0.5 mL	PSY-3002, PSY-3004
			0.75 mL	PSY-3002
			1 mL	PSY-3004
	04F01/F011		0.25 mL	PSY-3004
			0.5 mL	PSY-3001
			1 mL	PSY-3001
	05E27/F011		0.5 mL	PSY-1002

Formulation Number	Batch Number	Particle Size[a] (d_v50, µm)	Volume[b]	Clinical Study (R092670-)[c]
Early Research Formulations		(b) (4)		
F001	96J16/F001[e]		2 mL in vial	BEL-1[g] (eq. 50 mg/mL)
F002	98B16/F002[e]		2 mL in ampoule	BEL-2[g]
F004	98B18/F004[e]		2 mL in ampoule	BEL-2[g], BEL-4[g]
	99C16/F004[e]		1.5 mL in vial	BEL-7[g]
	01C09/F004[e]		1.5 mL in vial	INT-11[g]

Note: In PSY-3001 – no pharmacokinetic samples were collected, in other Phase 3 studies only sparse sampling for population pharmacokinetic analysis.

* F011 formulation, used in early Phase 1 and Phase 2 studies.

[a] Particle sizes as measured with a Malvern Mastersizer 2000 instrument or, if obtained with previous instruments, rescaled.

[b] Prefilled syringes unless otherwise indicated (vial or ampoule).

[c] 22G 1.5-inch safety needles were used, unless otherwise specified.

[d] Research formulation, not intended to be marketed

[e] Drug substance sterilized by (b) (4) Otherwise, drug substance sterilized by (b) (4)

[f] 22G 1.5-inch safety needles for gluteal injection and 23G 1-inch safety needles for deltoid injection.

[g] 21G 1.5-inch safety needles for gluteal and deltoid (USA-3 only) injection.

11. Is the IVIVC established?

The applicant conducted a study (PSY-1002), which was a multi-center, open-label, randomized, parallel-group study in subjects with schizophrenia to explore the relationship (IVIVC) between different paliperidone palmitate ER suspensions, particle sizes, in vitro dissolution rate, and in vivo release.

This study consisted of two periods. 143 subjects (schizophrenic patients) were randomized and 105 subjects completed both treatment periods. In Period 1, all subjects received a single intramuscular (i.m.) injection of a 1 mg paliperidone IR solution (Treatment A) in the gluteal muscle, and were subsequently randomly assigned to 1 out of 5 treatments (B, C, D, E, or F). Subjects who tolerated the i.m. paliperidone injection in Period 1 continued in Period 2 of the study, in which they received a single paliperidone palmitate 50 mg eq. injection in the gluteal muscle.

Single i.m. injections of paliperidone palmitate equivalent to 50 mg paliperidone were administered as the following treatments:

• Treatment B (Extra slow): d50= (b) (4) µm, batch 05E26/F013A;
• Treatment C (Slow): d50= (b) (4) µm, batch 05E26/F013B;
• Treatment D (Intermediate): d50= (b) (4) µm, batch 05E26/F013C [target, representative for phase 3];
• Treatment E (Fast): d50= (b) (4) µm, batch 05E26/F013D;
• Treatment F (Intermediate): d50= (b) (4) µm, batch 05E27/F011.

The in vitro release test is performed using USP Apparatus 2 (Paddle) at 50 rpm, 25°C in 900 mL of 0.001 M HCl containing 0.489% Polysorbate 20 (Tween®20).

Serial blood samples (up to 3000 hours (126 days) post dosing for treatments C, D, E and F and up to 6024 hours (252 days) post dosing for treatment B) were collected. Plasma samples were analyzed for paliperidone using LC/MS/MS techniques. Data from the 105 subjects who completed the study were used for the IVIVC.

The in vitro data were modeled by describing the observed fraction dissolved in vitro (represented by the subscript 1) for the ith dosage unit from the h^{th} batch at time t using

$$Y_{hi1}(t) = P_{h1}F_{h1}(t) + \varepsilon_{hi1}(t) \qquad \varepsilon_{hi1}(t) \sim N(0, \sigma_{h1}^2)$$

Where P_{h1} is a scale factor, $F_{h1}(t)$ is a fraction between 0 and 1 and $\varepsilon_{hi1}(t)$ is a random error term. The Weibull function was used to describe the shape of the dissolution curves as follows;

$$F_{h1}(t) = 1 - e^{-R_h(t)^{\psi_h}}$$

The in vivo (indicated by the subscript 2) measured paliperidone plasma concentration for the k^{th} subject at time t following administration of the ith dosage unit from the h^{th} batch was represented as follows

$$Y_{hi2k}(t) = P_2 Dose \int_0^t c_{\delta k}(t-\tau) F'_{hi2k}(\tau) d\tau + \varepsilon_{hi2k}(t) \qquad \varepsilon_{hi2k}(t) \sim N(0, \sigma_{h2}^2)$$

Where $c_{\delta k}(t)$ represents the unit impulse response function for the k^{th} subject, $F_{hi2k}(t)$ is the fraction dissolved from the ith dosage unit in vivo at time t and the prime denotes differentiation with respect to time. Concentration-time data available from an immediate release formulation were used to estimate the unit impulse response function for each subject. P2 takes into account the difference in relative bioavailability between the immediate and controlled release formulation. Variation between subjects was accounted for by writing

$$g(F_{hi2k}(t)) = g(F_{h2}(t)) + s_{hk} \qquad s_{hk} \sim N(0, \sigma_{hk}^2)$$

Where s_{hk} is a random effect associated with the k^{th} subject. The relationship between in vitro and in vivo fractions dissolved was modeled using a time scaling such that

$$F_{h2}(t) = F_{h1}(t^*)$$

Where t* is the scaled time corresponding to t. The relationship between t and t* was;

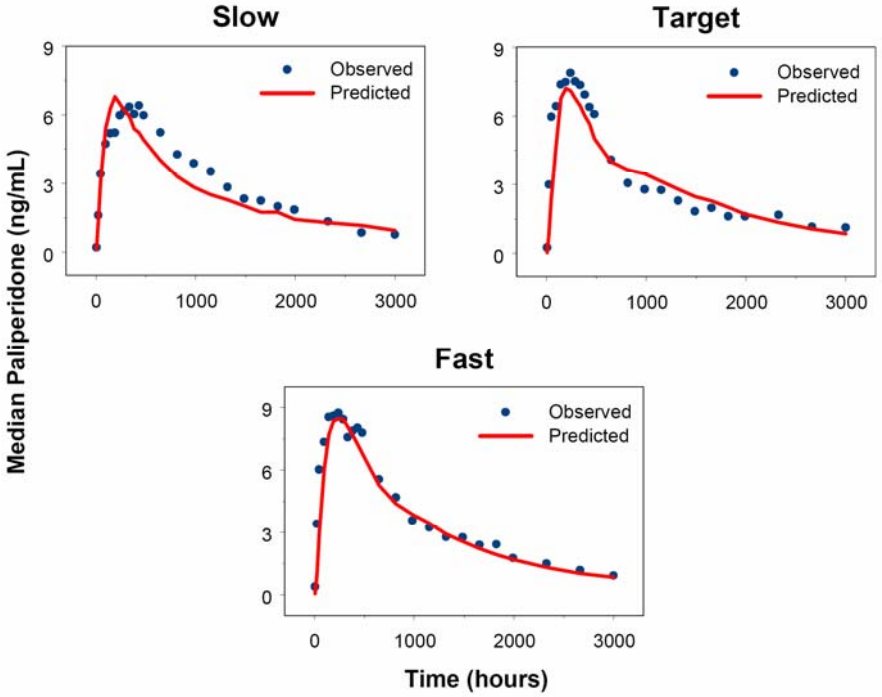
$$ln(t^*) = \theta_2 + \theta_3\, ln(t) + \theta_4\, ln(t)^2 + \theta_5\, ln(R_h)$$

Where the term with R_h is included to express the dependence of the time scaling on the fraction dissolved in vitro at t*.

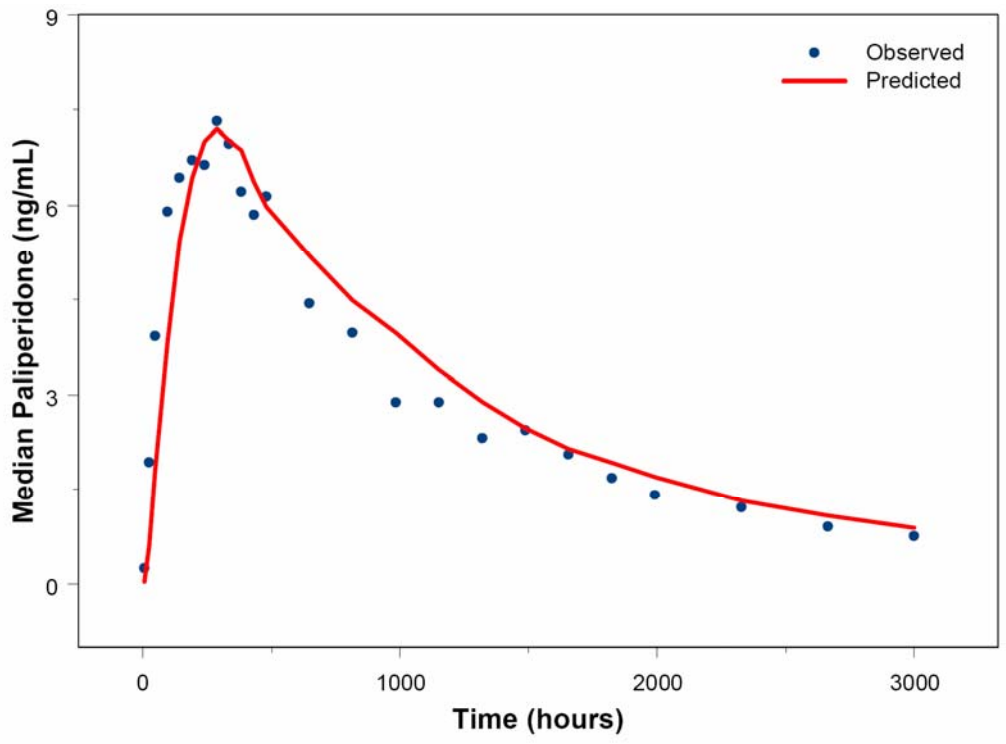
Following table shows the parameter estimates.

Parameter	θ_2	θ_3	θ_4	θ_5
Estimate	-19.4	3.99	-0.197	-0.943
Precision (%CV)	11	14	19	19

The following figure shows the median observed and median predicted paliperidone plasma concentration following an i.m administration of paliperidone palmitate slow, intermediate and fast 50 mg eq. using the IVIVC model.

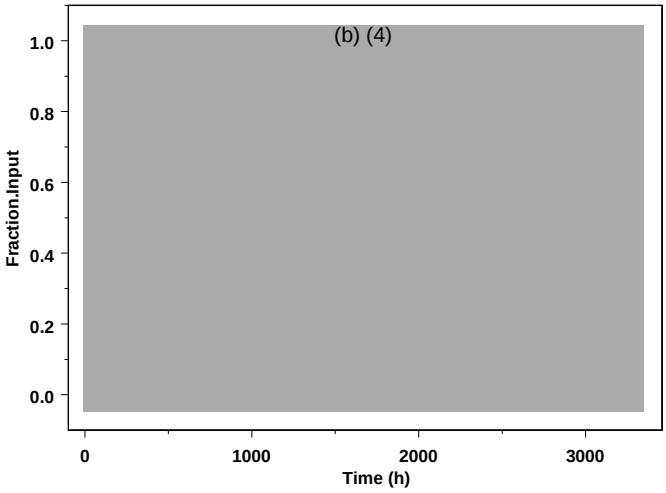


The following figure shows the median observed and median predicted paliperidone plasma concentration following an i.m administration of paliperidone palmitate intermediate (F011 formulation) 50 mg eq. using the IVIVC model.

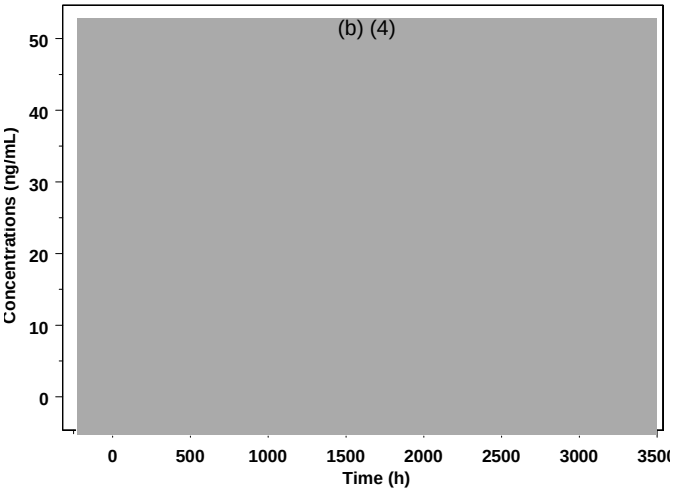


There are two major concerns regarding the IVIVC modeling practice. First of all, the variability of the in vivo behavior raised the concern of the model validity.

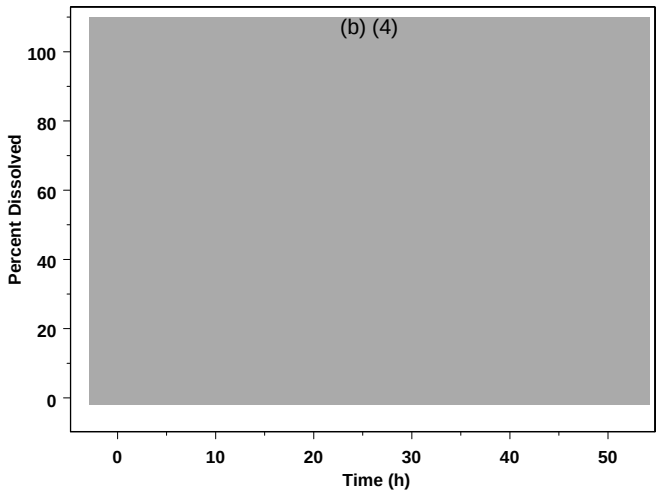
The comparison of the input rate among three batches is shown in the following figure. As shown, the accumulative inputs (obtained from deconvolution) of the three formulations overlap each other.



Similarly, the drug concentration profiles for these three batches also overlap as shown in the following figure.

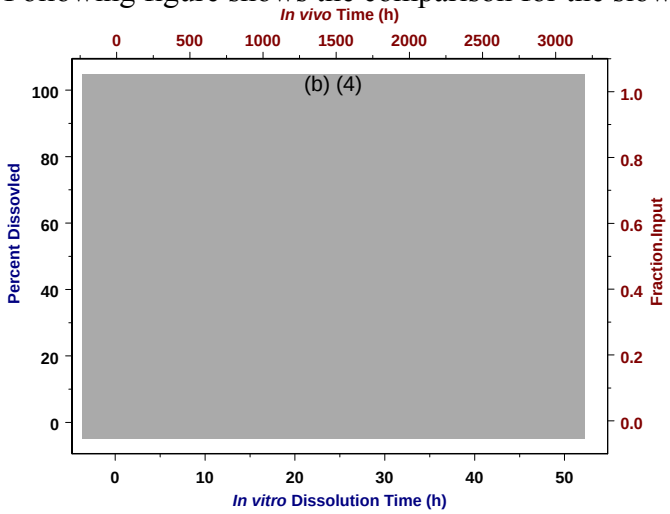


On the other hand, the in vitro release profiles of three batches separate nicely as shown in the following figure.

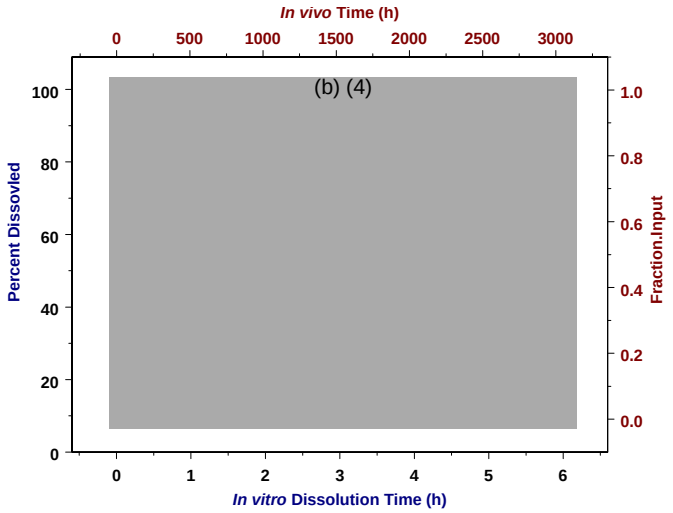


If comparing the inputs with the in vitro dissolved, the profiles do not match with each other as shown in the following figures.

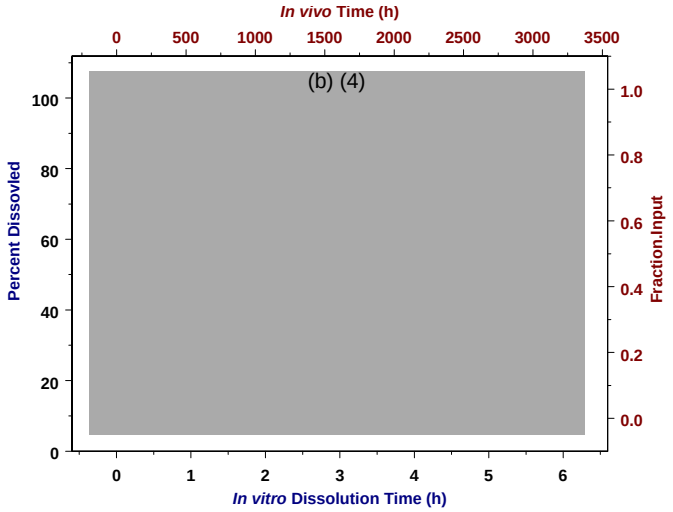
Following figure shows the comparison for the slow batch.



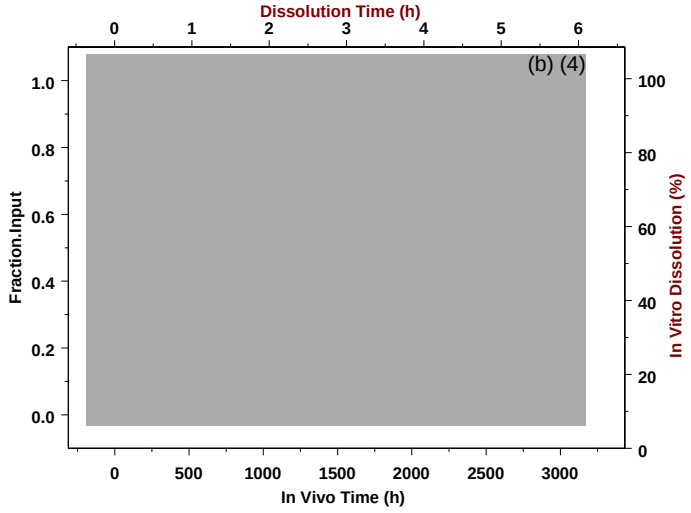
Following figure shows the comparison for the intermediate batch.



Following figure shows the comparison for the fast batch.



The following figure shows the comparison between in vitro dissolution and in vivo release for external validation batch.

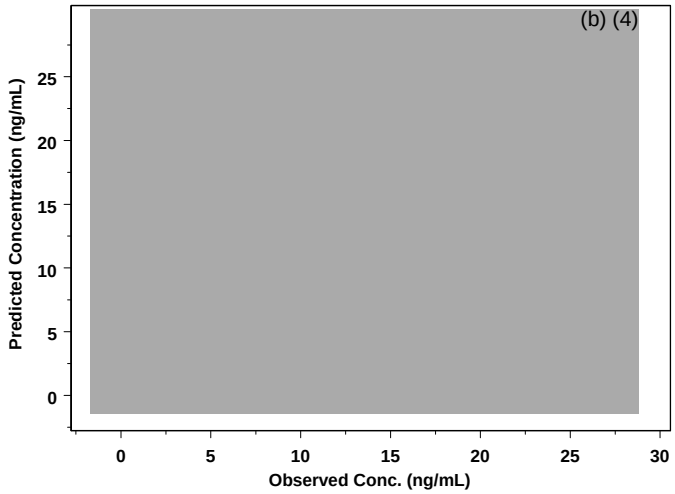


It is noted that not only the in vivo variability is large, but also the relationship between in vitro and in vivo is not linear if it exists. Therefore, the applicant's approaches seem reasonable by using nonlinear model and by using NONMEM program to take the variability into consideration.

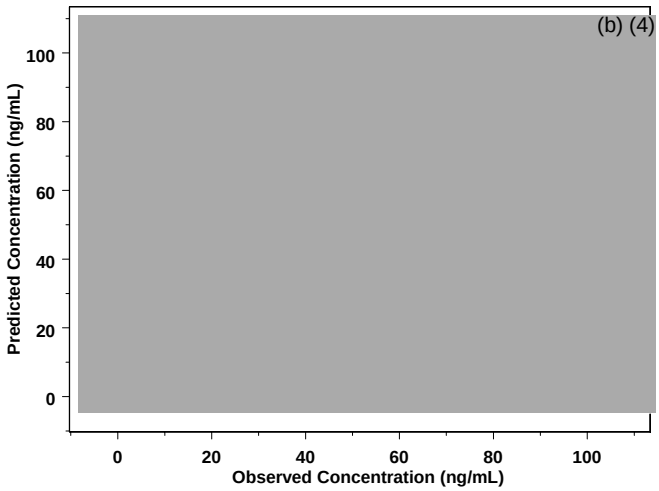
To take into consideration the large difference between dissolution profiles and the concentration profiles, two sets of scaling factors were utilized. One is the factor (P2) to account for the difference in bioavailability between the unit impulse response function (UIR) and the paliperidone palmitate formulations, which was estimated to be 1.415. Another set of factors, reflected in the following equation, links the in vitro times and the in vivo times.

$$ln(t^*) = \theta_2 + \theta_3\, ln(t) + \theta_4\, ln(t)^2 + \theta_5\, ln(R_h)$$

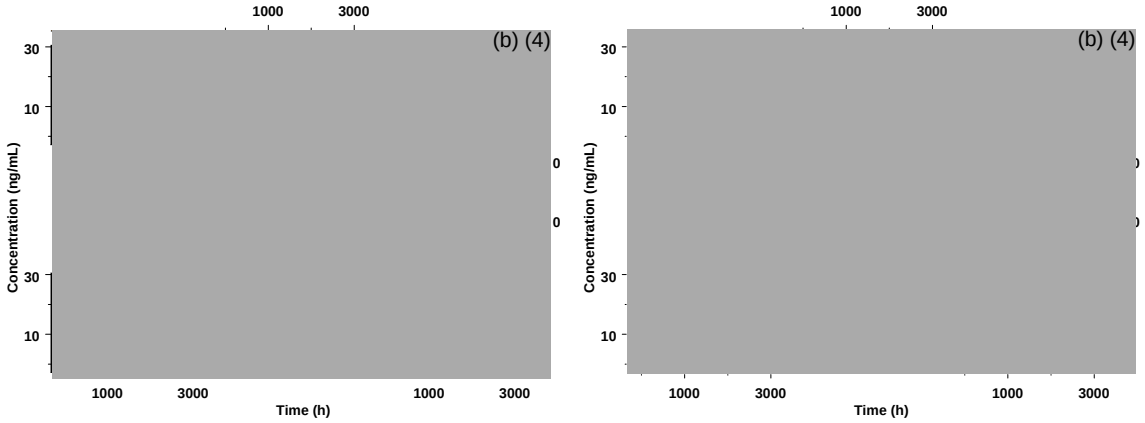
The model is evaluated by comparing the consistency between the observed and predicted concentrations. Following figure shows the comparison between observed concentrations and the model predicted concentrations for the external validation batch.



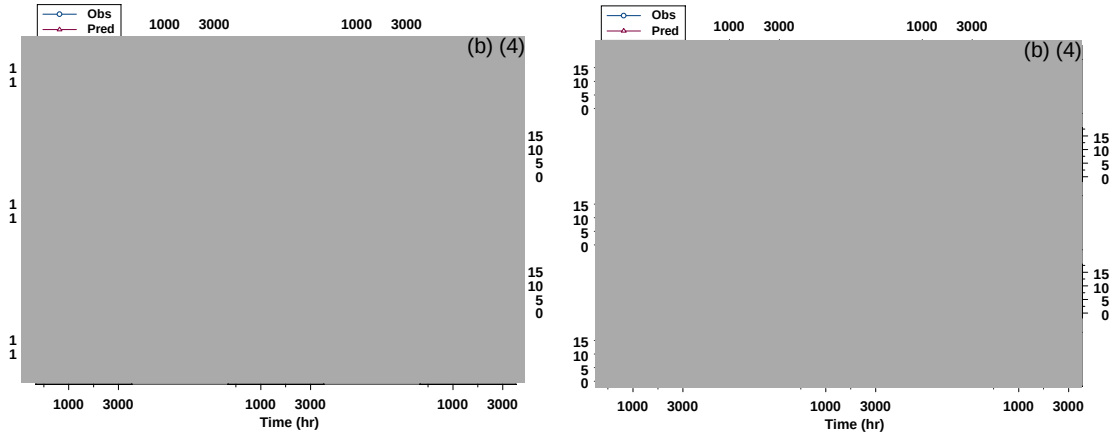
Similar plot for the 3 batches used in the model building process are shown below.



The observed concentration time profiles and the predicted curves for the external validation batch at individual level are shown in the following figures. As can be seen, most individuals match well while some of them mismatch.

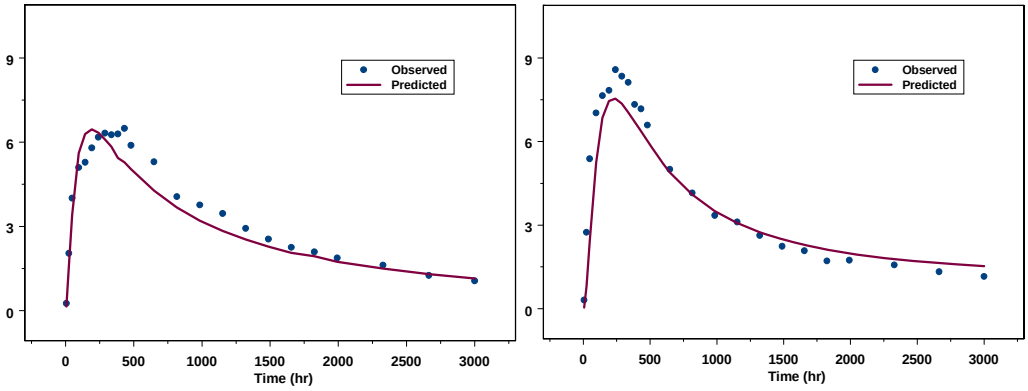


Similar plots are shown below for the batches used in model building process.

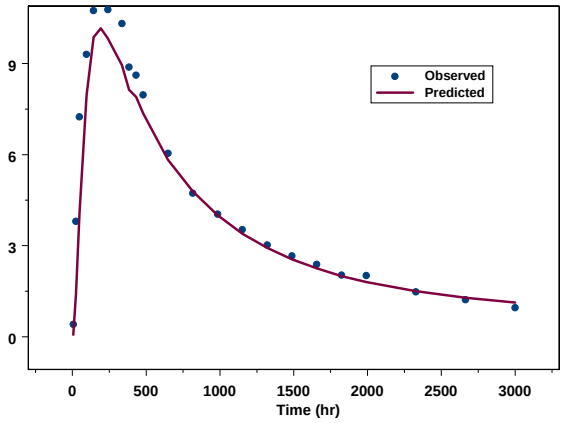


For the IVIVC model, the mean values are of concern. The applicant provided the plot for the observed and predicted concentrations using median values as shown previously.

The reviewer constructed the mean plots for the three batches shown in the following figures.



Slow Intermediate



Fast

Therefore, although at the individual level, for some subjects, the model predicted mismatches the observed, such as subject 27 and 111 shown in the above figures, the mean predictions generally match the mean observations.

The second concern is the prediction error, i.e., how well the matches are between the mean predictions and mean observations. The applicant used the median of the observed and predicted concentrations to calculate the Cmax and AUCt to generate the prediction errors. The reviewer recalculated these parameters using both the median and the mean concentrations. The following table shows the results.

		Using median			Using Mean		
Parameter	Formulation	Observed	Predicted	PE (%)*	Observed	Predicted	PE (%)
Cmax (ng/mL)	Slow	6.41	6.79	-5.94 (-5.60**)	6.49	6.46	0.54
	Target	7.87	7.20	8.52 (8.51**)	8.58	7.55	12.06
	Fast	8.73	8.43	3.41 (3.44**)	11.128	10.16	8.71
			Mean: |5.95| (|5.85*|)			***Mean |7.10|***	
AUCt (ng·h/mL)	Slow	8772	7736	11.81	9170	8374	8.68
	Target	8662	8451	2.44	9627	9517	1.14
	Fast	10340	9622	6.94	11434	10676	6.63
			Mean |7.06|			***Mean |5.48|***	

*PE: prediction error

**Applicant's results which are not consistent with reviewer's results

As shown, the average absolute percent prediction errors (%PE) are less than 10% for Cmax and AUC and the %PE for each formulation does not exceed 15%. These conclusions can be made either based on the median concentrations or the mean concentrations.

In addition, the external validation performed by the applicant also support the IVIVC model as shown in the following table.

Parameter	Formulation	Observed*	Predicted*	Prediction Error (%)
C_{max} (ng/mL)	F011	7.32	7.20	1.64
AUC_t (ng.h/mL)**	F011	8341	8957	-7.39

* Observed and predicted values are derived from the median observed and predicted profile, respectively.
** AUC_t= area under the plasma concentration-time curve from time 0 to t_{last} (=3000 hours)

Therefore, although the in vivo variability is large, the model made reasonable predictions on average. The IVIVC predictability has been established.
[

12. Is the proposed dissolution specification adequate?

Based on the developed and validated Level A IVIVC model for paliperidone palmitate, the following in-vitro release specifications are proposed. The 8-minute time point (b) (4), the 20-minute time point monitors the (b) (4), and the 45-minute time point assesses (b) (4) has been released. The proposed in vitro release specification ranges are shown in Table below.

Time (min)	Lower (%)	Target (%)	Upper (%)
8	(b) (4)		
20			
45			

The predicted PK parameters using the target, lower and upper in vitro release specifications are displayed the Table below.

	C_{max} (ng/mL)	AUC_t** (ng.h/mL)	AUC_∞ (ng.h/mL)	t_{max} (days)
Lower (L)				(b) (4)
Target (T)				
Upper (U)				
L/T***	0.89	0.94	0.97	
U/T***	1.06	1.04	1.02	
U/L***	1.18	1.10	1.06	

* Values are derived from the median predicted plasma concentration-time profile.
** AUC_t= area under the plasma concentration-time curve from time 0 to t_{last} (=3000 hours)
*** Ratio of Point Estimates

The impacts of switching from the target formulation to the formulation with upper or lower proposed release specifications, as well as switching from formulations with upper to lower proposed specifications and vice versa were simulated at steady-state. Non-parametric superposition to steady-state was performed, using the predicted paliperidone plasma concentrations, for the target formulation, and subsequently 28 days (one dosing interval) after the last dose, a switch was simulated (one dosing interval) using either the lower or upper proposed specification. The switch from target to either the upper or lower specification is summarized Table below.

	C_{max} (ng/mL)	AUC_τ (ng.h/mL)	t_{max} (days)
Target (ss)			(b) (4)
Target (ss) + switch to Lower Spec (L)			
Target (ss) + switch to Upper Spec (U)			
L/T**	0.95	0.96	
U/T**	1.01	1.01	

* Values are derived from the median predicted plasma concentration-time profile.
** Ratio of Point Estimates

Also, the upper end of the specification was simulated to steady-state followed by a switch to the lower end of the specification. Results are shown below.

	C_{max} (ng/mL)	AUC_τ (ng.h/mL)	t_{max} (days)
Upper Spec (ss)			(b) (4)
Upper Spec (ss) + switch to Lower Spec (L)			
L/U**	0.94	0.94	

* Values are derived from the median predicted plasma concentration-time profile.
** Ratio of Point Estimates

Similarly, the lower end of the specification was simulated to steady-state followed by a switch to the upper end of the specification. Results are shown below.

	C_{max} (ng/mL)	AUC_t (ng.h/mL)	t_{max} (days)
Lower Spec (ss)	(b) (4)		
Lower Spec (ss) + switch to Upper Spec (U)			
U/L**	1.05	1.05	

* Values are derived from the median predicted plasma concentration-time profile.
** Ratio of Point Estimates

According to the in vitro data for building IVIVC model, the descriptive statistics are calculated at each time point among the 12 units collected for the target formulation as shown in the following table.

Time (hr)	0.025	0.083	0.133	0.183	0.333	0.5	0.75	1	1.5	2
Min	(b) (4)									
1st Qu.										
Mean										
Median										
3rd Qu.										
Max										
Std Dev.	0.76	0.38	0.63	0.61	0.67	0.52	0.59	0.63	0.71	0.55
CV	6.54%	1.31%	1.58%	1.26%	1.03%	0.69%	0.70%	0.70%	0.75%	0.57%

In the table, the highlighted columns are for the applicant proposed time points of 8, 20 and 45 minutes, respectively.

Based on these data and the established IVIVC model, the proposed dissolution specification are acceptable as shown in the following table.

Parameter	**Proposed Dissolution Method and Specifications**
Apparatus type:	USP Type II
Media:	0.001 M HCl containing 0.489% Polysorbate 20 (Tween®20)
Volume:	900 ml
Temperature:	25 ± 0.5 °C
Frequency:	50 rpm
Sampling Times:	8, 20, and 45 minutes
Acceptance Criteria:	8 minutes (b) (4) of Label Claim 20 minutes (b) (4) of Label Claim 45 minutes (b) (4) of Label Claim
Analysis	HPLC UV detection

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5. APPENDIX II. Individual Study Synopsis

1. Comparative BA-BE study (R092670-PSY-1002)

Title of Study: Open-Label, Parallel, Randomized Study to Explore the In Vitro/In Vivo Correlation of Paliperidone Palmitate Long-Acting Formulations and the Comparability of the F011 and F013 Formulations in Subjects with Schizophrenia

Principal Investigator: I. Francetic, M.D., Ph.D. – Clinical Hospital Centre "Zagreb", Kispaticeva, Zagreb, Croatia

Study Period: August 18, 2005 to March 6, 2007

Objectives: The primary objective of this study was to explore the IVIVC of 4 paliperidone palmitate suspensions of F013 with different particle sizes (Treatments B, C, D, and E) after a single i.m. injection of paliperidone palmitate equivalent to 50 mg paliperidone (i.e., paliperidone palmitate 50 mg eq.). Treatment A (paliperidone IR solution) was used as a reference formulation during the development of the IVIVC model.

A secondary objective was to compare the exposure of the to-be-marketed intermediate-particle-size paliperidone palmitate formulation F013 (Treatment D) with that of the intermediate-particle-size paliperidone palmitate formulation F011 (Treatment F). Both formulations were used in Phase 3 studies. In addition, the safety and tolerability of paliperidone palmitate i.m. injections were evaluated in subjects with schizophrenia.

Subjects: It was planned that at least 140 subjects (25 subjects per treatment group, with 15 additional subjects in Treatment B to compensate for the higher dropout rates expected as the result of the longer post-treatment follow-up phase) would participate in this study. A total of 143 male and female subjects aged 20 to 65 years old with a diagnosis of schizophrenia received at least 1 dose of study drug with 40, 25, 25, 27, and 25 subjects assigned to Treatments B, C, D, E, and F, respectively. Each subject was expected to have a body mass index (BMI) between 17 and 35 kg/m^2 and a body weight of at least 50 kg. The subjects were otherwise healthy as confirmed by a pre-study physical examination, 12-lead ECG, vital signs, and clinical laboratory tests.

Study Design: This was a multi-center, open-label, randomized, parallel-group study in subjects with schizophrenia. The study consisted of a screening phase (within 21 days before the first i.m. injection of the study drug), an open-label treatment phase, and end-of-study evaluations upon completion of all the study procedures on Day 126 (for Treatments C, D, E, and F) or Day 252 (for Treatment B) or at the time of early withdrawal.

Paliperidone palmitate suspensions of formulation F013 with different particle sizes and release rates were used in this study. Single i.m. injections (gluteal muscle) equivalent to 50 mg paliperidone were administered as the following treatments:

- Treatment B: Release rate extra-slow, specific surface area (SSA) = 2 m^2/g, particle size (b) (4) nm, batch 05E26/F13A
- Treatment C: Release rate slow, SSA 5-7 m^2/g, particle size (b) (4) nm, batch 05E26/F13B
- Treatment D: Release rate intermediate, SSA ~ 9.5 m^2/g, particle size (b) (4) nm, batch 05E26/F13C
- Treatment E: Release rate fast, SSA = 12 m^2/g, particle size (b) (4) nm, batch 05E26/F13D
- Treatment F: F011, a suspension that does not contain (b) (4) The same dose (50 mg eq.) and route of administration (i.m. injection, gluteus) were used: Treatment F Release rate intermediate, SSA ~ 9.5 m^2/g, particle size (b) (4) nm, batch 05E27/F011
- The reference therapy (Treatment A) consisted of a single i.m. injection of a paliperidone immediate release solution at a dose of 1 mg (batches 05F16/F024 and 05J28/F024).

In Period 1, all subjects received a single i.m. injection of a 1 mg paliperidone immediate release solution (Treatment A) in the gluteal muscle and were assigned to Treatment B or randomly assigned to 1 of 4 treatment groups (C, D, E, or F). Only subjects who tolerated the i.m. paliperidone injection in Period 1 were enrolled into Period 2 of the study, in which they received a single paliperidone palmitate 50 mg eq. injection in the gluteal muscle: Treatments B, C, D, and E (i.e., formulations of F013 with different particle sizes) and Treatment F (formulation F011 with intermediate particle size). There was a washout phase of at least 7 days but no longer than 21 days between the i.m. injection in Period 1 and the i.m. injection in Period 2.

Serial blood samples (up to 3000 hours (126 days) post dosing for treatments C, D, E and F and up to 6024 hours (252 days) post dosing for treatment B) were collected. Plasma samples were analyzed for paliperidone using LC/MS/MS techniques. Data from the 105 subjects who completed the study were used for the IVIVC.

Based on the individual plasma concentration-time data, the following pharmacokinetic parameters were estimated for paliperidone: Cmax, tmax, λz, t1/2, AUC0-28d, AUClast, $AUC\infty$, CL/F, and F_{rel}. Paliperidone plasma concentration data from the paliperidone solution (Period 1) were used as a reference formulation during the calculations of the IVIVC model. The paliperidone plasma concentration data from the paliperidone long-acting injectables were used to explore an IVIVC model for these formulations.

Safety evaluations included physical examinations at screening and at the end of the study, vital sign measurements, clinical laboratory tests, ECGs, monitoring of extrapyramidal symptoms, and the recording of adverse events throughout the study. The subjects' psychiatric symptoms and a global clinical impression of symptom severity

were documented using the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) and the Clinical Global Impressions Scale (CGI-S). The injection site was evaluated by the subject using a self-administered visual analog scale (VAS), and by the investigator.

Participation in the pharmacogenomics component of the study was optional. At screening or prior to i.m. paliperidone injection on Day 1 of Period 1, approximately 10 mL of whole blood was collected for genetic analysis from subjects who gave informed consent for this part of the study. DNA collection was performed to allow for the genotyping of candidate genes involved in: 1) the metabolism of paliperidone palmitate, 2) the response to paliperidone palmitate, or 3) schizophrenia. No genes were genotyped during this study. Genotyping of any genes in the future will be reported in a separate report.

Descriptive statistics by treatment were used to summarize paliperidone plasma concentrations for each sampling time and for its pharmacokinetic parameters, including AUC0-28d, AUC∞, AUClast, Cmax, tmax, t1/2 and F_{rel}. Mean, median and individual paliperidone plasma concentration-time profiles were plotted by treatment.

To compare the relative bioavailability of the 2 intermediate-particle-size formulations F011 (Treatment F) and F013 (Treatment D), an analysis of variance (ANOVA) was performed to calculate the mean treatment ratios (F013/F011) for AUC (AUC0-648h, AUC∞ and AUClast) and Cmax and their 90% confidence intervals after a single dose. A general linear model (GLM) with formulation as a factor was fitted to natural-log transformed pharmacokinetic parameter estimates. The least squares means and the mean squared error from the ANOVA model were used to construct 90% confidence intervals on the natural-log scale and back transformed to original scale for interpretation. Data from subjects who prematurely discontinued from the study were included in the analysis provided their pharmacokinetic parameters could be estimated.

The development of an IVIVC model was presented in a separate report, combining the in vitro dissolution data with the in vivo pharmacokinetic data from this study.

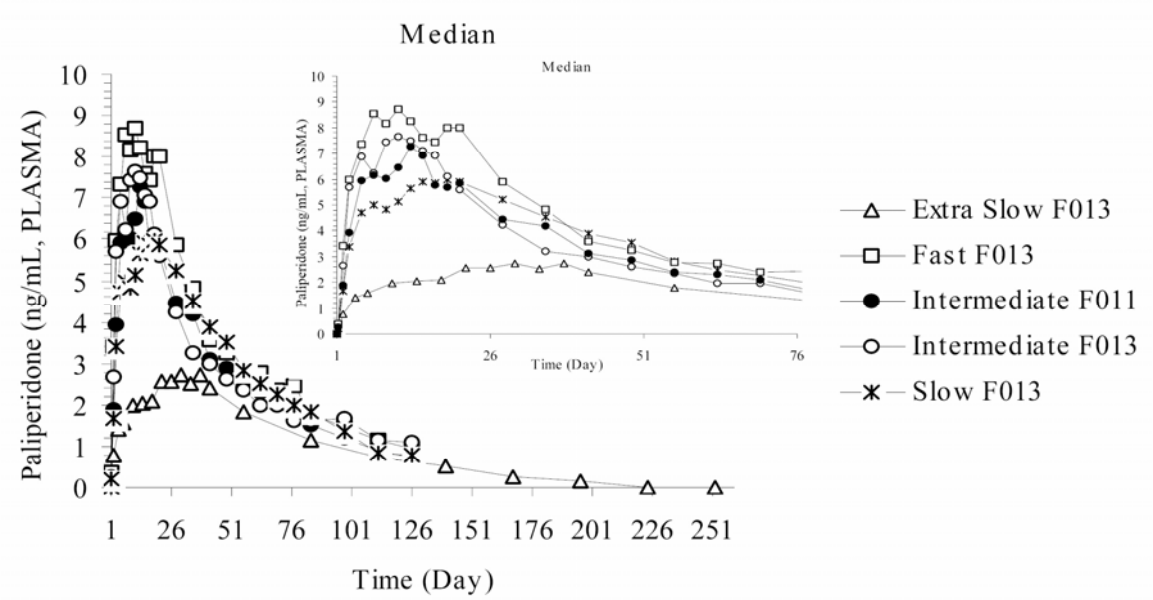
Incidences of treatment emergent abnormalities were tabulated. Descriptive statistics were calculated by injection site, dose, and time point for all psychiatric and clinical laboratory parameters. Effects on cardiovascular variables were evaluated by means of descriptive statistics and frequency tabulations. Body weight, BMI, pulse rate, and blood pressure were summarized by time point and treatment using descriptive statistics. Abnormal findings in the physical examination at screening and at the end of the study were listed and not otherwise evaluated statistically.

Results

Paliperidone plasma levels were determined using LC-MS/MS method. The following table shows the assay performance.

Species	LLOQ	Range	QC	samples	Calibration	standards
	(ng/mL)	(ng/mL)	Accuracy (%)	Precision (CV%)	Accuracy (%)	Precision (CV%)
R076477	0.10	0.2-250	0.4 to 1.9	3.7 to 5.6	-2.0 to 3.0	2.5 to 6.0

The review for the development of an IVIVC model is presented in a separate section. The median plasma concentration profile for different treatments of 50 mg eq. paliperdone are presented below.



A comparison of the PK parameters of different treatments with 50 mg eq. paliperidone palmitate is given in Table below.

Parameters		Extra Slow (F013) (B)	Slow (F013) (C)	Intermediate (F013) (D)	Fast (F013) (E)	Intermediate (F011) (F)
C_{max}, ng/mL	Mean ± SD (n)	4.39 ± 3.03 (n=29)	7.36 ± 3.16 (n=22)	9.91 ± 5.59 (n=25)	12.80 ± 9.08 (n=26)	9.54 ± 5.99 (n=23)
	Median	3.62	7.27	9.40	9.66	7.82
t_{max}, days	Median	29.00	16.00	12.07	11.50	12.07
	(min - max)	(3.05 – 55.02)	(4.03 – 42.04)	(3.00 – 49.00)	(2.00 - 34.00)	(6.00 - 49.00)
AUC_{last}, ng.h/mL	Mean ± SD (n)	5595 ± 3668 (n=35)	9039 ± 2948 (n=23)	9317 ± 4005 (n=25)	11228 ± 3494 (n=26)	9775 ± 4288 (n=24)
	Median	4809	9677	8176	10921	8550
t_{last}, days	Median	139.00	125.00	125.00	125.03	125.00
	(min - max)	(10.00 – 259.00)	(58.08 – 127.08)	(62.00 – 127.05)	(41.00 – 134.04)	(58.00 – 130.04)
apparent $t_{1/2}$, days	Mean ± SD (n)	35.00 ± 20.40 (n=24)	27.66 ± 10.11 (n=13)	35.27 ± 12.01 (n=17)	29.90 ± 13.20 (n=21)	28.15 ± 10.58 (n=17)
	Median	30.70	24.04	34.38	29.89	30.45
AUC_{∞}, ng.h/mL	Mean ± SD (n)	6828 ± 3800 (n=24)	10303 ± 1912 (n=13)	11992 ± 4531 (n=17)	12901 ± 3335 (n=21)	11408 ± 4527 (n=17)
	Median	7111	10752	9992	12551	9435

The relative bioavailability of paliperidone after injection of 50 mg eq. paliperidone palmitate of F013 (Treatment D) versus the F011 (Treatment F) are shown in the following table.

Parameter	Treatment Group	N	Geometric L.S. Means (*)	90% CI	Estimated Ratio (%)(*) (F013/F011)	90% CI
$AUC_{0\text{-}648h}$	INTERMEDIATE F013 (D)	25	3582.75	(2920.94; 4394.51)		
	INTERMEDIATE F011 (F)	24	3912.11	(3176.06; 4818.75)	91.58	(68.40; 122.61)
AUC_{last}	INTERMEDIATE F013 (D)	25	8491.88	(7376.37; 9776.09)		
	INTERMEDIATE F011 (F)	24	9063.19	(7849.80; 10464.14)	93.70	(76.62; 114.58)
AUC_{inf}	INTERMEDIATE F013 (D)	17	11259.88	(9720.37; 13043.21)		
	INTERMEDIATE F011 (F)	17	10707.18	(9243.23; 12402.97)	105.16	(85.42; 129.47)
C_{max}	INTERMEDIATE F013 (D)	25	8.40	(6.90; 10.22)		
	INTERMEDIATE F011 (F)	23	8.17	(6.66; 10.03)	102.77	(77.38; 136.48)

(*) Data analyzed on log scale, but statistics transformed back to original scale

Comparing the different release rate formulations of F013, the median paliperidone peak plasma concentrations (Cmax) after injection of 50 mg eq. paliperidone palmitate varied between 3.62 and 9.66 ng/mL. The median time (tmax) to reach peak plasma concentrations after injection of 50 mg eq. paliperidone palmitate varied between 11.50 and 29.00 days. Especially after injection with the extra-slow release formulation (F013) (Treatment B), paliperidone peak plasma concentrations were reached later than with the other formulations, with a median tmax of 29.00 vs. 11.50-16.57 days.

The median Cmax and tmax after injection of 50 mg eq. paliperidone palmitate tended to decrease (Cmax) and are obtained later (tmax) with increasing particle sizes (i.e. the larger the particle size, the slower the release rate).

The median apparent half-life values (range 24.04-34.38 days) were comparable after injection of 50 mg eq. paliperidone palmitate formulations with different particle sizes.

Adverse Events: During Period 1 (after the 1 mg paliperidone i.m. injection), 64 subjects (45%) reported at least 1 treatment-emergent adverse event. The most commonly reported adverse events were sedation (6%), orthostatic hypotension (5%), insomnia (5%), and injection site pain (5%). During Period 2 (after the 50 mg eq. i.m. injection), 80 subjects (58%) reported at least 1 treatment-emergent adverse event. The most commonly reported adverse events were nasopharyngitis (8%), injection site pain (7%), headache (7%), and psychotic disorder (5%). There were no noteworthy or clinically significant differences in the incidence of treatment-emergent adverse events when comparing the 50 mg eq. treatments (extra-slow, slow, intermediate, and fast release rates) and formulations (F011 and F013) to each other.

Subjects With Adverse Events

Treatment	A	B	C	D	E	F
N	143 [a]	38	23	25	26	25
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
One or more adverse events	64 (45)	23 (61)	14 (61)	12 (48)	15 (58)	16 (64)
One or more serious adverse events[b]	0 (0)	5 (13)	1 (4)	1 (4)	2 (8)	2 (8)
Deaths	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinuations due to adverse events	1 (1)	7 (18)	0 (0)	0 (0)	0 (0)	0 (0)

[a] One subject was not randomized to a treatment in Period 2. Six subjects randomized to a treatment in Period 2 were not administered study drug.
[b] Excludes 1 subject with a serious adverse event resulting in a screening failure prior to study drug administration.

Comments

1. The median Cmax decreases and tmax is obtained later with increasing particle size, which is consistent with the hypothesis that particle size is driving the release rate.
2. Although the point estimates suggest that paliperidone exposure (AUC, Cmax) after injection of paliperidone palmitate is similar between the intermediate release F013 formulation and the intermediate release F011 formulation, the bioequivalence between these two formulations has not been shown.

2. Dose proportionality study (R092670-PSY-1004)

Title of Study: Open-Label, Parallel, Randomized, Dose Proportionality Pharmacokinetic Study of Paliperidone after Intramuscular Injection of Paliperidone Palmitate in the Deltoid or Gluteal Muscle in Subjects with Schizophrenia

Investigator and study site: (b) (4)

Study Period: June 30, 2005 - September19, 2006

Objectives: The primary objective of this study was to evaluate the dose proportionality of the to-be-marketed formulation of paliperidone palmitate equivalent to 25, 50, 100, and 150 mg paliperidone, following an intramuscular (i.m.) injection in the gluteal or deltoid muscles.

The secondary objective was to compare the pharmacokinetic profiles of paliperidone palmitate at the 2 injection sites.

In addition, the safety and tolerability of paliperidone palmitate i.m. injections were evaluated.

Subjects: It was planned that at least 200 subjects (25 subjects per treatment group, and 8 treatment groups in total) would participate in this study. Two hundred-one male and female subjects (23 to 28 in each of 8 treatment groups) aged 20 to 64 years old with a diagnosis of schizophrenia were enrolled in this study.

Study design: This was a single-dose, open-label, randomized, parallel-group study. It consisted of 3 periods: a screening period of up to 21 days prior to drug administration, an open-label treatment period consisting of a single i.m. injection of paliperidone palmitate, and a 126-day post treatment observation period. End-of-study evaluations were completed on Day 126 or at early withdrawal.

Paliperidone palmitate suspension made available in prefilled syringes (100 mg eq./mL) for intramuscular injection. Formulation F013 (batch 05C24/F013) was used in this study. Paliperidone ER tablets (3 mg) for oral administration, Formulation F016 (batch 426909) was used in this study.

Blood samples for pharmacokinetics were collected on the following days during the 126-day observation period: 1, 2, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 28, 35, 42, 49, 56, 63, 70, 77, 84, 98, 112, and 126. Concentrations of the enantiomers of paliperidone (R078543 (+) and R078544 (-)) in plasma were determined. The total paliperidone concentration was calculated as the sum of both enantiomers. Based on the individual plasma concentration-time data, the following pharmacokinetic parameters were estimated for paliperidone and its enantiomers: Cmax, tmax, λz, t1/2, AUC0-28d,

AUClast, AUC∞ and CL/F. The ratios of (+)/(-) paliperidone plasma concentrations, Cmax and AUC∞ were calculated. Additionally, the unbound pharmacokinetic parameters Cmax,u, AUC∞,u and CLu/F were estimated.

The occurrence of adverse events was documented in the CRF. Psychiatric evaluations (PANSS and CGI-S) were performed at screening, before drug administration on Day 1, on Day 28, and at the end of study or early withdrawal. Clinical laboratory tests, EPS, and ECG evaluations were performed at screening, on Days 1, 15, and 28, and at end of study or at early withdrawal. Vital signs and injection site evaluations were performed at various time points throughout the study.

Participation in the pharmacogenomics component of the study was optional. At screening or prior to i.m. paliperidone palmitate injection on Day 1, approximately 10 mL of whole blood was collected for genetic analysis from subjects who gave informed consent for this part of the study.

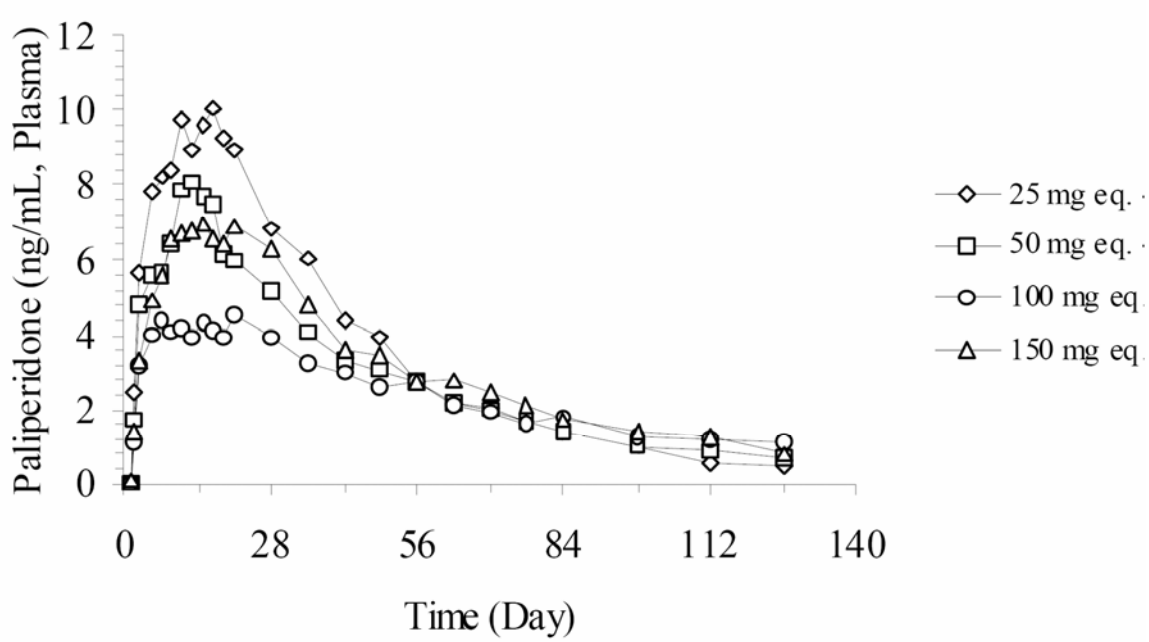
Descriptive statistics were calculated by injection site (deltoid or gluteal) and by dose (25, 50, 100 and 150 mg eq.) for all pharmacokinetic parameter estimates as well as for the plasma concentrations at each sampling time point. As the primary pharmacokinetic analysis, the dose proportionality of paliperidone palmitate injections was evaluated in dose-normalized pharmacokinetic parameters (Cmax and AUC∞) for paliperidone using a linear regression model and pairwise comparison. The secondary pharmacokinetic analysis compared the deltoid group with the gluteal group. An analysis of variance (ANOVA) was performed to calculate the mean treatment ratios (deltoid/gluteal for AUC∞ and Cmax) and their 90% confidence intervals. Incidences of treatment emergent abnormalities were tabulated. Descriptive statistics were calculated by injection site, dose, and time point for all psychiatric and clinical laboratory parameters.

Results:

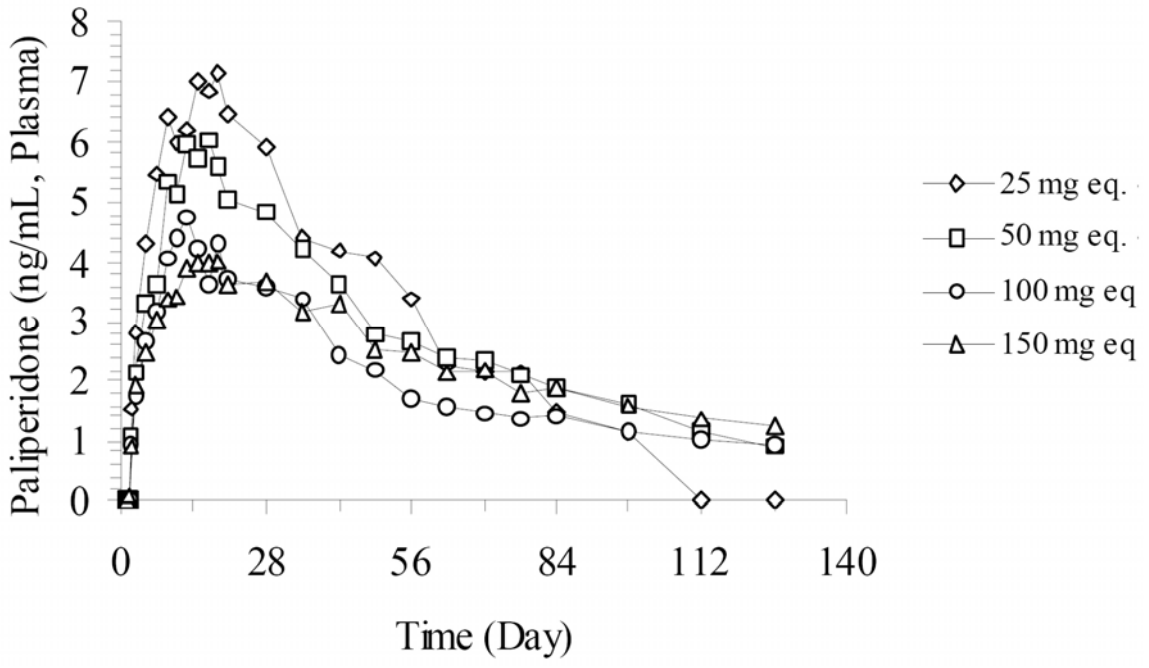
Enantiomers of paliperidone (R078543 and R078544) plasma levels were determined using LC-MS/MS method. The following table shows the assay performance.

Species	LLOQ	Range	QC	samples	Calibration	standards
	(ng/mL)	(ng/mL)	Accuracy (%)	Precision (CV%)	Accuracy (%)	Precision (CV%)
R078543	0.20	0.2-100	-1.5 to 1.9	3.4 to 7.6	-1.0 to 2.0	2.1 to 3.2
R078544	0.20	0.2-100	-1.1 to 1.2	4.3 to 5.6	-0.7 to 1.5	2.4 to 4.4

The median dose-normalized (to 50 mg eq.) plasma concentration-time profiles at deltoid injection site for the 4 different doses are presented in Figure below.



The median dose-normalized (to 50 mg eq.) plasma concentration-time profiles at gluteal injection site for the 4 different doses are presented in Figure below.



A summary of the median PK parameters (dose-normalized to 50 mg eq.) is presented in Table below.

Deltoid				
PK parameter	25 mg eq. (n)	50 mg eq. (n)	100 mg eq. (n)	150 mg eq. (n)
t_{max}, days[a]	13.01 (22)	13.00 (23)	12.51 (22)	14.00 (21)
C_{max}, ng/mL	11.0 (22)	8.79 (23)	5.33 (22)	9.17 (21)
AUC_{last}, ng.h/mL	10266 (22)	9445 (19)	7754 (22)	9574 (17)
AUC_{∞}, ng.h/mL[b]	11271(20)	11162 (18)	9311 (16)	11170 (18)
$t_{1/2}$, days[a]	24.9 (20)	29.1 (18)	43.7 (16)	40.6 (18)
Gluteal				
PK parameter	25 mg eq. (n)	50 mg eq. (n)	100 mg eq. (n)	150 mg eq. (n)
t_{max}, days[a]	16.00 (21)	13.41 (24)	14.12 (25)	17.03 (24)
C_{max}, ng/mL	8.70 (21)	6.85 (24)	5.35 (25)	5.06 (24)
AUC_{last}, ng.h/mL	9779 (20)	8978 (21)	5966 (21)	7329 (20)
AUC_{∞}, ng.h/mL[b]	10557 (19)	10088 (19)	9652 (18)	10442 (16)
$t_{1/2}$, days[a]	25.1 (19)	31.2 (19)	40.0 (18)	49.1 (16)

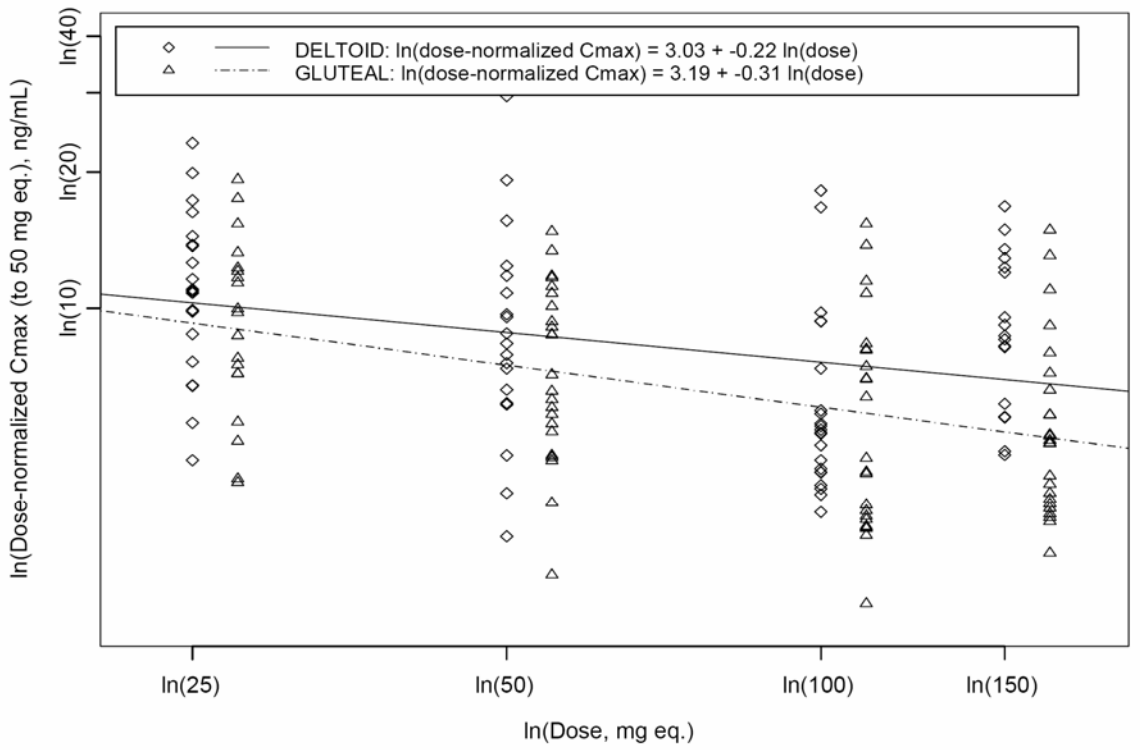
[a] Calculated on the actual concentration-time data
[b] The number of subjects with %AUC extrapolated > 20% increased with dose

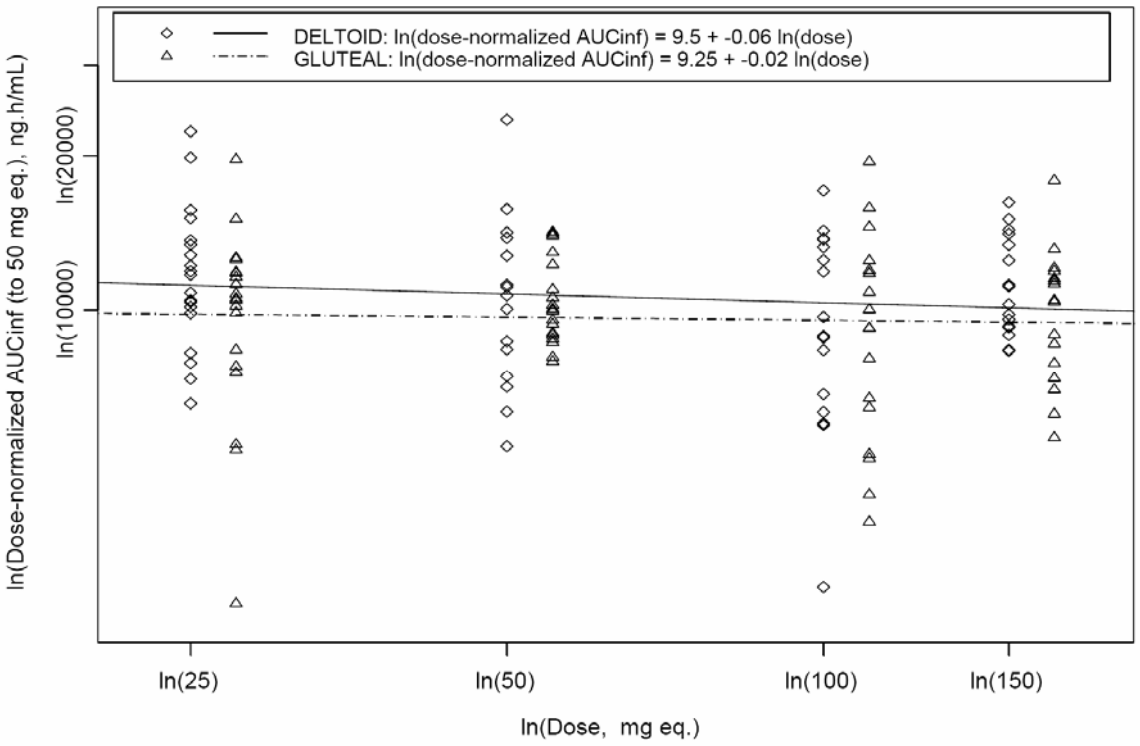
A summary of the comparison of the geometric mean exposure parameters (Cmax and AUC∞) of paliperidone for each dose between deltoid and gluteal, performed on log-transformed data, is shown in the following table.

Dose	Parameter	Ratio % (Deltoid/gluteal)	90% CI (Original Scale)
25 mg eq.	AUCinf (ng.h/mL)	117.83	(96.63; 143.69)
	Cmax (ng/mL)	119.85	(96.20; 149.30)
50 mg eq.	AUCinf (ng.h/mL)	104.38	(88.38; 123.27)
	Cmax (ng/mL)	119.91	(93.41; 153.92)
100 mg eq.	AUCinf (ng.h/mL)	103.00	(79.02; 134.26)
	Cmax (ng/mL)	108.75	(84.61; 139.78)
150 mg eq.	AUCinf (ng.h/mL)	114.43	(97.64; 134.11)
	Cmax (ng/mL)	164.85	(131.21; 207.12)

Data analyzed on log-scale and results transformed back to the original scale

Paliperidone palmitate dose proportionality was primarily assessed by applying a linear regression model, for each injection site separately, between the log-transformed dose-normalized (to 50 mg eq.) AUC∞ and Cmax vs. log-transformed dose (Figure below).





For AUC∞ the slopes were not significantly different from zero for both the deltoid (slope -0.06, p=0.36) and gluteal (slope -0.02, p=0.76) injection sites indicating a proportional increase in AUC∞ with dose (hypothesis was not rejected at the 5% significance level) as shown in the following table.

For Cmax the slopes were significantly different from zero for both the deltoid (slope -0.22, p=0.0062) and gluteal (slope -0.31, p<0.0001) injection sites, indicating a less than proportional increase in Cmax with dose as shown in the following table.

Injection Site	Parameter	Slope	95% CI	P-value
Deltoid	AUCinf (ng.h/mL)	-0.06	(-0.18; 0.07)	0.3606
	Cmax (ng/mL)	-0.22	(-0.37; -0.06)	0.0062
Gluteal	AUCinf (ng.h/mL)	-0.02	(-0.15; 0.11)	0.7575
	Cmax (ng/mL)	-0.31	(-0.46; -0.16)	<.0001

The linear regression model indicated a proportional increase in AUC∞ and a less than proportional increase in Cmax with dose.

Pairwise comparisons of log-transformed dose-normalized (to 50 mg eq.) AUC∞ and Cmax between all dose groups were made for each injection site separately. Estimated ratios of geometric means between all pairs of doses along with associated 90% CI are given in table below.

Injection Site	Parameter	Dose(Test)	Dose(Ref)	Ratio % (Test/Ref)	90% CI
Deltoid	AUCinf (ng.h/mL)	25 mg eq.	100 mg eq.	124.65	(102.43; 151.69)
		25 mg eq.	150 mg eq.	103.14	(84.75; 125.51)
		25 mg eq.	50 mg eq.	106.88	(88.11; 129.64)
		50 mg eq.	100 mg eq.	116.63	(95.12; 143.00)
		50 mg eq.	150 mg eq.	96.50	(78.70; 118.32)
		100 mg eq.	150 mg eq.	82.74	(67.28; 101.77)
	Cmax (ng/mL)	25 mg eq.	100 mg eq.	182.50	(145.75; 228.50)
		25 mg eq.	150 mg eq.	123.11	(96.76; 156.62)
		25 mg eq.	50 mg eq.	125.30	(99.52; 157.75)
		50 mg eq.	100 mg eq.	145.65	(115.68; 183.38)
		50 mg eq.	150 mg eq.	98.25	(76.83; 125.65)
		100 mg eq.	150 mg eq.	67.46	(53.02; 85.82)
Gluteal	AUCinf (ng.h/mL)	25 mg eq.	100 mg eq.	106.42	(87.11; 130.00)
		25 mg eq.	150 mg eq.	98.31	(79.97; 120.86)
		25 mg eq.	50 mg eq.	92.04	(75.55; 112.13)
		50 mg eq.	100 mg eq.	115.63	(94.65; 141.25)
		50 mg eq.	150 mg eq.	106.82	(86.89; 131.32)
		100 mg eq.	150 mg eq.	92.38	(74.95; 113.87)
	Cmax (ng/mL)	25 mg eq.	100 mg eq.	165.38	(130.03; 210.34)
		25 mg eq.	150 mg eq.	169.12	(133.28; 214.59)
		25 mg eq.	50 mg eq.	125.19	(98.43; 159.22)
		50 mg eq.	100 mg eq.	132.10	(104.76; 166.58)
		50 mg eq.	150 mg eq.	135.09	(107.39; 169.93)
		100 mg eq.	150 mg eq.	102.26	(81.29; 128.64)

Data analyzed on log-scale and results transformed back

The Cmax of paliperidone was in general higher after a single-dose injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle (mean ratio

for the dose groups ranged from 108.75% to 164.85%) whereas this difference was much less pronounced for AUC∞, (mean ratio for the dose groups ranging from 103.00% to 117.83%).

In total, 120 subjects (60%) experienced 1 or more treatment-emergent adverse events. The most common adverse events were tachycardia (10%), headache (7%), schizophrenia (6%), insomnia (5%), and weight increase (5%). Eighteen subjects (9%) reported 1 or more treatment-emergent serious adverse events. The most commonly reported serious adverse events were psychiatric disorders (7%). Five subjects prematurely withdrew from the study due to adverse events. No subject died due to an adverse event. Nine subjects (4%) reported treatment-emergent adverse events at the site of injection (6 associated with gluteal injection and 3 with deltoid injection). On Days 15, 28, and at end of study, 1, 2, and 4 subjects, respectively, had a population-specific linear derived corrected QT intervals (QTcLD) above 450 ms. Twenty subjects (10%) experienced treatment-emergent orthostatic hypotension at least once during the study. There were no clinically relevant differences between the treatment groups in the EPS rating scales.

Comments:

1. The data indicate that the AUC∞ of paliperidone increased proportionally with dose after single-dose injections of 25 mg eq. to 150 mg eq. paliperidone palmitate in both the deltoid and gluteal muscle. The increase of the peak plasma concentrations (C_{max}) was less than dose proportional for both injections sites at doses greater than 50 mg eq.
2. The C_{max} of paliperidone was generally higher after single-dose injection of paliperidone palmitate in the deltoid muscle compared to the gluteal muscle whereas this difference was less pronounced for AUC∞.
3. After i.m. injection in the deltoid or gluteal muscle, median half-life (reflecting the absorption rate for this type of formulations) increased with dose from 25 days after the 25 mg eq. dose to 40-49 days after the 100 and 150 mg eq. doses. Median half-lifes were comparable between injection sites.

3. IVIVC Study based on R092670-PSY-1002

Study title: Development of an in Vitro - in Vivo Correlation and its Validation for Paliperidone Palmitate.

Objectives:

- to develop a validated Level A IVIVC model for paliperidone palmitate,
- to demonstrate the bio-relevance of the in vitro dissolution method,
- to consequently apply the IVIVC model to justify bio-relevant in vitro release rate specifications for the to-be-marketed formulation (F013).

Study design:

The study design was stated in comparative BA study R092670-PSY-1002. Data from the 105 subjects who completed the study were used for the IVIVC.

The in vitro data were modeled by describing the observed fraction dissolved in vitro (represented by the subscript 1) for the ith dosage unit from the hth batch at time t using

$$Y_{hi1}(t) = P_{h1}F_{h1}(t) + \varepsilon_{hi1}(t) \qquad \varepsilon_{hi1}(t) \sim N(0, \sigma^2_{h1})$$

Where P_{h1} is a scale factor, $F_{h1}(t)$ is a fraction between 0 and 1 and $\varepsilon_{hi1}(t)$ is a random error term. The Weibull function was used to describe the shape of the dissolution curves as follows;

$$F_{h1}(t) = 1 - e^{-R_h(t)^{\psi h}}$$

The in vivo (indicated by the subscript 2) measured paliperidone plasma concentration for the k^{th} subject at time t following administration of the i^{th} dosage unit from the h^{th} batch was represented as follows

$$Y_{hi2k}(t) = P_2 Dose \int_0^t c_{\delta k}(t-\tau) F'_{hi2k}(\tau) d\tau + \varepsilon_{hi2k}(t) \qquad \varepsilon_{hi2k}(t) \sim N(0, \sigma^2_{h2})$$

Where $c_{\delta k}(t)$ represents the unit impulse response function for the k^{th} subject, $F_{hi2k}(t)$ is the fraction dissolved from the i^{th} dosage unit in vivo at time t and the prime denotes differentiation with respect to time. Concentration-time data available from an immediate release formulation were used to estimate the unit impulse response function for each subject. P2 takes into account the difference in relative bioavailability between the immediate and controlled release formulation. Variation between subjects was accounted for by writing

$$g(F_{hi2k}(t)) = g(F_{h2}(t)) + s_{hk} \qquad s_{hk} \sim N(0, \sigma^2_{hk})$$

Where s_{hk} is a random effect associated with the kth subject. The relationship between in vitro and in vivo fractions dissolved was modeled using a time scaling such that

$$F_{h2}(t) = F_{h1}(t^*)$$

Where t* is the scaled time corresponding to t. The relationship between t and t* was;

$$ln(t^*) = \theta_2 + \theta_3\, ln(t) + \theta_4\, ln(t)^2 + \theta_5\, ln(R_h)$$

Where the term with R_h is included to express the dependence of the time scaling on the fraction dissolved in vitro at t*.

The following table gives an overview of the formulations used in the Level A IVIVC model building and validation.

Formulation and Dose	Usage
IR paliperidone solution 1 mg	Model building & UIR
Slow PP** 50 mg eq. (F013, d_{50}= (b) (4)µm)	Model building & Internal validation
Intermediate PP 50 mg eq. (F013, d_{50}= (b) (4)µm)	Model building & Internal validation
Fast PP 50 mg eq. (F013, d_{50}= (b) (4)µm)	Model building & Internal validation
Intermediate PP 50 mg eq. (F011, d_{50}= (b) (4)µm)	External validation

**PP = Paliperidone Palmitate

The in vitro release test is performed using USP Apparatus 2 (Paddle) at 50 rpm, 25°C in 900 mL of 0.001 M HCl containing 0.489% Polysorbate 20 (Tween®20).

A two-compartment model with first order absorption was fitted to the individual paliperidone plasma concentration-time data observed following i.m. administration of IR paliperidone from study PSY-1002. Each subject's pharmacokinetic parameters were estimated separately using NONMEM VI. These individual parameter estimates were used to define each subject's unit impulse response, $c_{\delta k}(t)$ which was used in equation above. Median values of the different PK parameters were 4.72 h^{-1} (Ka), 120 L (Vd), 0.0432 h^{-1} (Kel), 0.0283 h^{-1} (K23) and 0.0629 h^{-1} (K32).

The model described above was fitted to the in vitro and in vivo data simultaneously using a custom-written PRED subroutine for NONMEM. All model fitting was carried out at the individual subject/dosage unit level.

For the internal validation of the model, the median observed paliperidone plasma concentration-time profile was compared to the median paliperidone plasma concentration-time profile predicted from the IVIVC model. The internal predictability of

the IVIVC was established by calculating the percent prediction error (% PE) for AUCt and Cmax derived from the median observed profile and median predicted profile for the three formulations.

% PE = [(Observed Value – Predicted Value)/Observed Value] x 100

For the external validation of the IVIVC model of paliperidone palmitate, intermediate formulation F011 (treatment F) was used. The same dose (50 mg eq.) and route of administration (i.m. injection in the gluteal muscle) were used. The following process was used:

- The Weibull parameters for the in vitro dissolution of intermediate formulation F011 were estimated by fitting the model to the in vitro dissolution data collected for this batch using NONMEM VI.

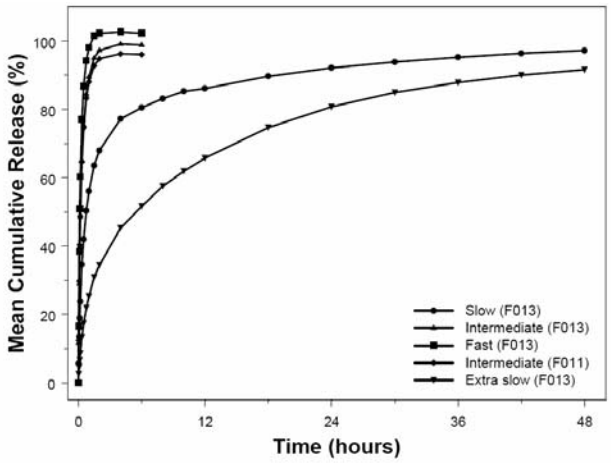
- These parameter estimates along with all other parameter estimates for the IVIVC model were used to predict paliperidone plasma concentrations for each subject who received intermediate formulation F011.

- As the study used a parallel group design, no information was available regarding the random subject effect (ε_{hk}) for those subjects having received intermediate formulation F011 other than that contained in the data for this particular batch. Consequently these random effects were estimated using these data and subsequently used in calculating predicted plasma drug concentration data for intermediate formulation F011.

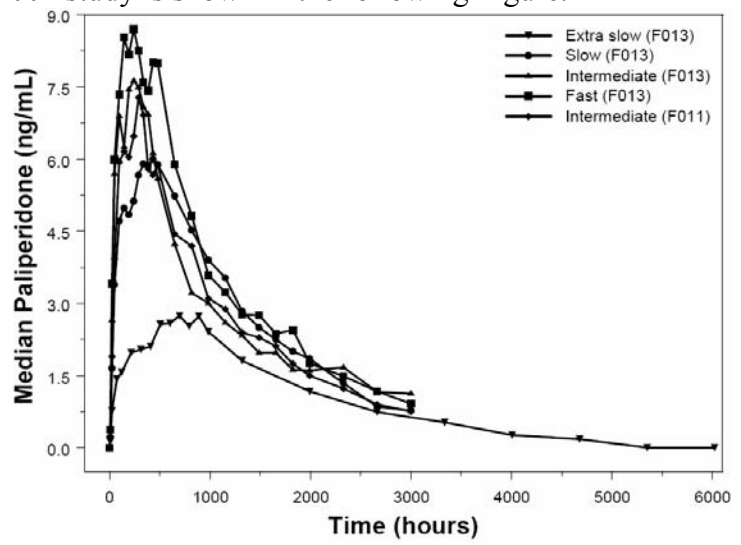
- The external predictability of the IVIVC was established by calculating the percent prediction error (% PE) for AUCt and Cmax derived from the median observed profile and median predicted profile.

Results

The following figure shows the cumulative in vitro release data for the four paliperidone palmitate formulations (Extra Slow, Slow, Intermediate and Fast PP 50 mg eq.) used in study PSY-1002.



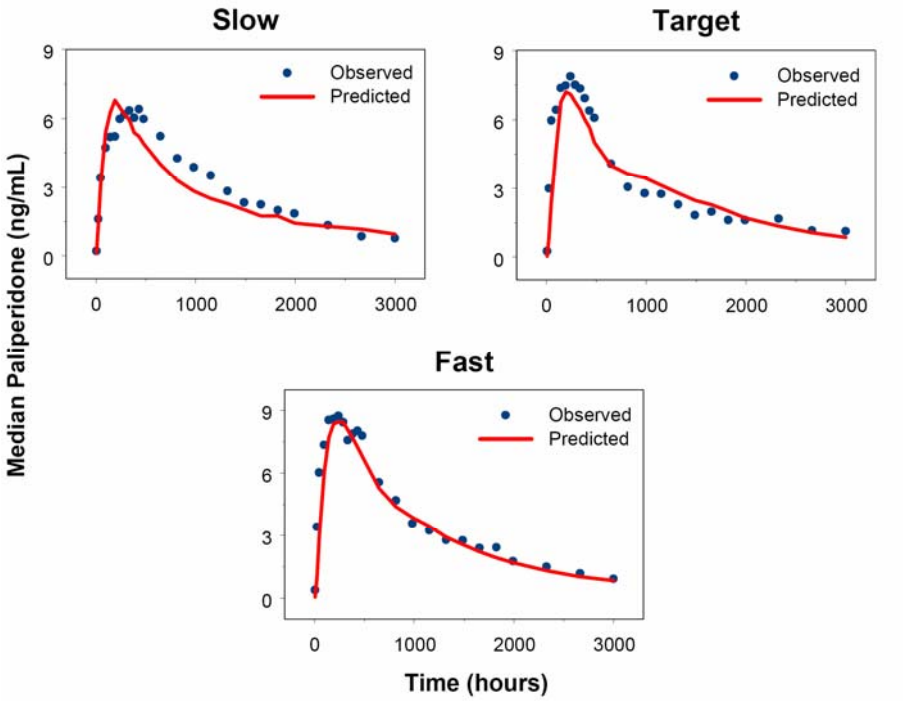
A median concentration-time plot for the different treatments administered in the PSY-1002 study is shown in the following Figure.



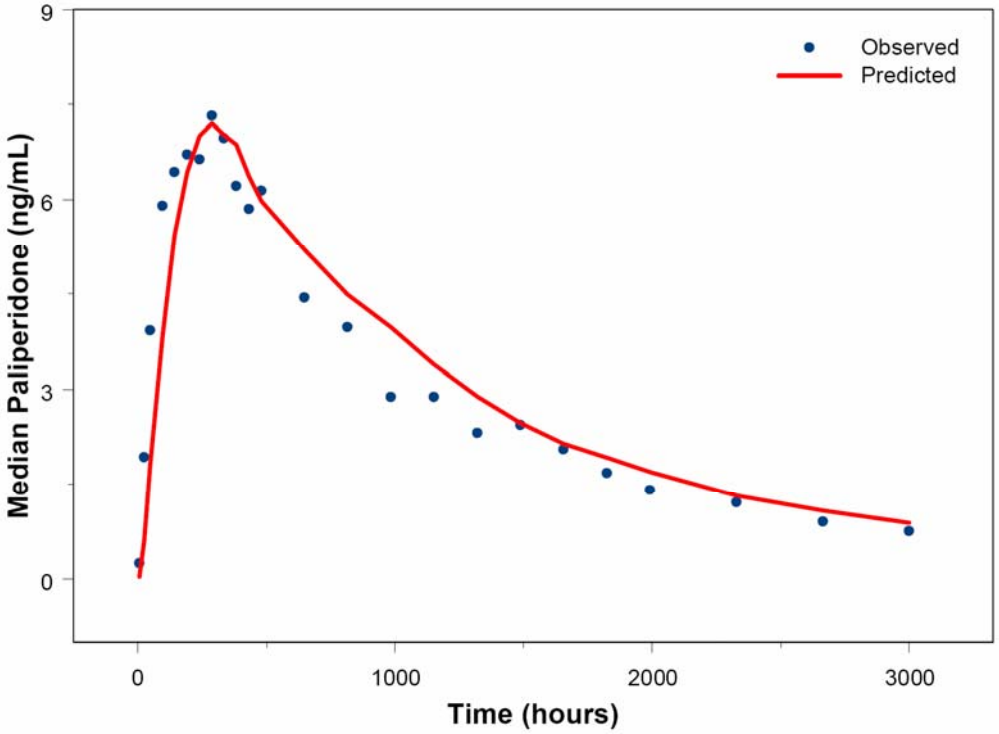
Following table shows the parameter estimates.

Parameter	θ_2	θ_3	θ_4	θ_5
Estimate	-19.4	3.99	-0.197	-0.943
Precision (%CV)	11	14	19	19

The following figure shows the median observed and median predicted paliperidone plasma concentration following an i.m administration of paliperidone palmitate slow, intermediate and fast 50 mg eq. using the IVIVC model.



The following figure shows the median observed and median predicted paliperidone plasma concentration following an i.m administration of paliperidone palmitate intermediate (F011 formulation) 50 mg eq. using the IVIVC model.



The internal predictability of IVIVC model is shown in the following table.

Parameter	Formulation	Observed*	Predicted*	Prediction Error (%)
C_{max} (ng/mL)	Slow	6.41	6.79	-5.60
	Target	7.87	7.20	8.51
	Fast	8.73	8.43	3.44
			Mean	***|5.85|***
AUC_t (ng.h/mL)**	Slow	8772	7736	11.81
	Target	8662	8451	2.44
	Fast	10340	9622	6.94
			Mean	***|7.06|***

* Observed and predicted values are derived from the median observed and predicted profile, respectively.
** AUC_t= area under the plasma concentration-time curve from time 0 to t_{last} (=3000 hours)

The external predictability of IVIVC model is shown in the following table.

Parameter	Formulation	Observed*	Predicted*	Prediction Error (%)
C_{max} (ng/mL)	F011	7.32	7.20	1.64
AUC_t (ng.h/mL)**	F011	8341	8957	-7.39

* Observed and predicted values are derived from the median observed and predicted profile, respectively.
** AUC_t= area under the plasma concentration-time curve from time 0 to t_{last} (=3000 hours)

Comments:

1. The mean should be used instead of median when comparing the observed and predicted concentrations.
2. Although the variability is of concern, generally speaking the IVIVC has been established.

4. Multiple dose study using formulation F4 (R092670-BEL-7)

Study Title: Open, multiple dose trial in 60 schizophrenic subjects exploring the pharmacokinetics, tolerability and safety following various dosing regimens of 9-hydroxy-risperidone palmitate (R092670) i.m.

Objective: to explore the pharmacokinetics of the F4 formulation following various multiple dosing regimens (loading dose and more frequent dosing during the first month) of intramuscularly injected 9-hydroxy-risperidone palmitate (R092670), aimed at attaining steady state of 9-hydroxy-risperidone within a time frame of 1 month and to document safety and tolerability of the different dosing regimens.

Investigators and study sites: (b) (4)

Trail period: August 17, 1999 to March 6, 2000

Subjects: Male or female; aged between 18 to 55 (panels III and V) or 65 (panels I, II and IV) years, extremes included.

Study Design: This is an open, multiple dosing trial in 4 panels of 10 (Panels I, II, IV, V) and 1 panel of 20 (Panel III) schizophrenic subjects with the depot i.m. formulation R092670.

- Panel I: 100 mg-eq. 9-hydroxy-risperidone i.m., followed by 3 monthly injections of 50 mg.
- Panel II: 200 mg-eq. 9-hydroxy-risperidone i.m., followed by 3 monthly injections of 100 mg.
- Panel III: 300 mg-eq. 9-hydroxy-risperidone i.m. (as two injections, one in each buttock) followed by 3 monthly injections of 150 mg.
- Panel IV: 50 mg-eq. 9-hydroxy-risperidone i.m., followed 1 week later by 4 monthly injections of the same dose.
- Panel V: 150 mg-eq. 9-hydroxy-risperidone i.m., followed 1 week later by 4 monthly injections of the same dose.

Panel I, II and III were treated preferentially on Days 1, 29, 57 and 85 and Panel IV and V on Days 1, 8, 36, 64 and 92 (one day earlier or one day later) between 8 and 9 a.m. Allocation to panel depended on the dose of current neuroleptic medication: subjects on low dose (2 mg-eq. risperidone) to Panel I or IV and subjects on higher dose (4-6 mg-eq. of risperidone) to any panel. There were 4 (Panels I, II and III) or 5 (Panel IV and V) injections. Blood samples were taken at the following time points:

Panels I, II and III

- Injection 1 (Day 1): immediately before (predose) and at 8, 24, 48, 72 and 96 hours after the 1st injection, and on Days 8, 11, 15 and 22 of the trial at the same time of the day as the last injection.

- Injection 2 (Day 29): immediately before (predose) and one week after the 2nd intramuscular injection (ie, trial Day 36) at the same time of the day as the last injection.
- Injection 3 (Day 57): immediately before (predose) and one week after the 3rd intramuscular injection (ie, trial Day 64) at the same time of the day as the last injection.
- Injection 4 (Day 85): immediately before (predose) and at 8, 24, 48, 72 and 96 hours after the 4th injection and on Days 92, 95, 99, 106 and 113 of the trial at the same time of the day as the last injection.

Panels IV and V

- Injection 1 (Day 1): immediately before (predose) and at 8, 48 and 96 hours after the 1st injection.
- Injection 2 (Day 8): immediately before (predose) and at 8, 24, 48, 72 and 96 hours after the 2nd injection, and on Days 15, 18, 22 and 29 of the trial at the same time of the day as the last injection.
- Injection 3 (Day 36): immediately before (predose) and one week after the 3rd intramuscular injection (ie, trial Day 43) at the same time of the day as the last injection.
- Injection 4 (Day 64): immediately before (predose) and one week after the 4th intramuscular injection (ie, trial Day 71) at the same time of the day as the last injection.
- Injection 5 (Day 92): immediately before (predose) and at 8, 24, 48, 72 and 96 hours after the 5th injection and on Days 99, 106, 113 and 120 of the trial at the same time of the day as the last injection.

$C_{predose}$, C_{min}, C_{max}, t_{max}, λz, AUC_{τ}, dose normalized-AUC_{τ}, $C_{ss,av}$, FI of 9-hydroxy-risperidone were determined by standard non-compartmental methods. Achievement of steady state following the various dosing regimens was graphically explored by composite plots of the individual concentration profiles per panel. An explorative analysis to determine which subjects were poor and extensive metabolizers of CYP2D6 was performed.

Descriptive statistics for pharmacokinetic, laboratory and cardiovascular parameters and tabulation of adverse events, physical examination results and injection site evaluations/subject opinion.

Results:

Concentrations of 9-hydroxy-risperidone in plasma were determined using a radioimmunoassay procedure with an LOQ of 0.20 ng/mL. The assay validation is shown below.

LOQ (ng/mL)	Range (ng/mL)	QC sample	
		Precision (CV%)	Accuracy (%)
0.20 or 4.0*	0.20-10 or 4.0-200*	2.8 to 5.2	7.3 to 16.6

*dependent on sample valumes

Following table shows the demographic data for this trial.

Baseline characteristics - subject disposition	All subjects (Panels I to V)[a]
Number of subjects entered (M/F)	60 (36/24)
Distribution subjects over panels	Panel I, II, IV and V: n=10, Panel III: n=20
Age: median (min-max), yrs	39.0 (22.0-63.0)
Weight: median (min-max), kg	80.5 (49.0-115.0)
Height: median (min-max), cm	170.5 (143.0-193.0)
Race: Caucasian / Other	51 / 9 (all in Panel III)
Discontinuation of treatment - reason	2[b] - withdrawal of consent

a) The panels were comparable with respect to age, weight and height, but not for gender and race: Panels III, IV and V were more or less balanced for gender, Panel I consisted of 2 females and 8 males and Panel II of 0 females and 10 males. All subjects in Panels I, II, IV and V were Caucasian, in Panel III, 9 of the 20 subjects were of another race.

b) Subject #30008 from Panel II (immediately after the 1st injection) and subject #30122 from Panel IV (immediately after the 3rd injection).

Following table summarizes the pharmacokinetic paramters.

Summary of the pharmacokinetic parameters (median values)

PARAMETER		**PANEL**				
		I (N=10)	II (N=9)	III (N=20)	IV (N=10/9)*	V(N=10)
First injection (dose)		100 mg	200 mg	300 mg	50 mg	150 mg
C_{max}	ng/mL	12.1	20.8	38.0	18.4	62.5
t_{max}	h	240.01	239.37	240.00	335.94	301.00
t_{max}	days	10.0	10.0	10.0	14.0	12.5
AUC_{τ}	ng.h/mL	4886	11459	17616	9507	23000
AUC_{35d}	ng.h/mL	-	-	-	10829	27454
Last injection (dose)		50 mg	100 mg	150 mg	50 mg	150 mg
C_{min}	ng/mL	10.5	23.3	26.8	9.71	24.8
C_{max}	ng/mL	18.0	35.8	50.5	24.1	56.1
t_{max}	h	84.14	96.45	95.79	95.55	71.80
t_{max}	days	3.5	4.0	4.0	4.0	3.0
AUC_{τ}	ng.h/mL	9172	20111	25108	10808	27265
dn-AUC_{τ}***	ng.h/mL	18343	20111	16739	21616	18177
C_{max}/C_{min}		1.75	1.54	1.91	2.34	2.55
$C_{ss,av}$	ng/mL	13.7	29.9	37.4	16.1	40.6
FI	%	55.6	44.3	63.7	93.1	85.8

* First injection: N=10, last injection: N=9.
** Panel I, II, III : $AUC_{day\ 1\text{-}28}$; Panel IV, V : $AUC_{day\ 8\text{-}35}$
*** Normalized to a dose of 100 mg.

The dosing schedule of the R092670 depot formulation (F4) was as follows:
Panel I: 100 mg-eq. 9-hydroxy-risperidone i.m., followed by 3 monthly injections of 50 mg.
Panel II: 200 mg-eq. 9-hydroxy-risperidone i.m., followed by 3 monthly injections of 100 mg.
Panel III: 300 mg-eq. 9-hydroxy-risperidone i.m. followed by 3 monthly injections of 150 mg.
Panel IV: 50 mg-eq. 9-hydroxy-risperidone i.m., followed 1 week later by 4 monthly injections of the same dose.
Panel V: 150 mg-eq. 9-hydroxy-risperidone i.m., followed 1 week later by 4 monthly injections of the same dose.

Median predose concentrations

DAY	**9-hydroxy-risperidone predose concentration (ng/mL)**				
Panel I-III (Panel IV-V)	Panel I 50 mg	Panel II 100 mg	Panel III 150 mg	Panel IV 50 mg	Panel V 150 mg
(8)	-	-	-	8.45	26.2
29 (36)	6.00	13.6	21.9	10.5	18.4
57 (64)	8.84	17.2	24.3	9.15	25.9
85 (92)	9.46	22.0	28.2	11.2	28.0
113 (120)	12.9	26.2	31.6	10.5	30.6

The most frequently reported adverse events (≥ 10 subjects) were injection site reaction (31 subjects), weight increase (18 subjects), injection site pain (13 subjects), insomnia (11 subjects) and anxiety (10 subjects). Subject #30107 was hospitalized for severe psychosis (verbatim: deterioration of psychosis), starting 22 days after the 4th injection with 50 mg-eq. 9-hydroxy-risperidone, and was considered doubtfully drug-related. The subject recovered after 1 week. Subject #30112 was hospitalized for moderate melaena and GI haemorrhage, starting 21 days after 5th injection with 50 mg-eq. 9-hydroxy-risperidone, and was considered to be doubtfully drug-related. The subject recovered after 4 days. Other severe adverse events were: weight increase (12 kg) after the 5th injection with 50 mg-eq. 9-hydroxy-risperidone in subject #30114 from Panel IV (probably drug-related) and injection site reaction in left side after the 2nd injection with 150 mg-eq. 9-hydroxy-risperidone in subject #30116 from Panel V (very likely drug-related).

Comments:

1. This study used formulation F4, which is not the to-be-marketed formulation.
2. The study showed that the steady-state had not been reached after 4 monthly injecitons.

*5. **Multiple dose study comparing formulation F11 to F4 (R092670-INT-11)***

Study Title: Double-blind, multiple-dose study in schizophrenic volunteers exploring the comparative pharmacokinetics, tolerability and safety following i.m. injections of paliperidone palmitate (R092670) originating from 2 different production methods.

Objective: To explore the pharmacokinetics of paliperidone palmitate produced according to a new production method (F11) and to compare these results with those of paliperidone palmitate produced according to the previous method (F4). In addition, the safety and tolerability of the 2 formulations were to be documented.

Investigators and study sites: (b) (4)

Trail period: Clinical Conduct: May 14, 2001- February 6, 2002 Sample analysis: August 8, 2001 –February 20, 2002 (paliperidone) August 16, 2001 –March 14, 2002 (paliperidone palmitate).

Subjects: 60 subjects with schizophrenia were male or female (of non-childbearing potential or with adequate contraception), aged between 18 to 65 years, with normal weight (body mass index between 15 and 35), diagnosis of axis I schizophrenia of any subtype according to DSM-IV, and healthy on the basis of a prestudy physical examination, medical history, electrocardiogram, the results of blood biochemistry, hematology, serology, and urinalysis.

Study Design: This was a multiple-dose, double-blind, randomized, crossover Phase 1 study in 2 panels of 30 subjects with schizophrenia to investigate 2 formulations of paliperidone palmitate at 2 dose levels. Each subject was to be assigned to a specific dose level (Panel I or Panel II) by the investigator and was to receive a total of 4 i.m. injections (2 i.m. injections per formulation) in a randomized crossover fashion with an interval of 1 month.

Panel I: 4 i.m. doses of 50 mg-eq. paliperidone;
Panel II: 4 i.m. doses of 150 mg-eq. paliperidone.

In each panel, the subjects were randomized to a treatment sequence and received 2 single i.m. injections of the F11 formulation followed by 2 single i.m. injections of the F4 formulation, or vice versa, in a double-blind fashion.

The safety, tolerability, and pharmacokinetics of paliperidone and of its palmitate ester after each of the injections were to be documented over a 25-week period.

Blood samples for analysis of paliperidone and paliperidone palmitate in plasma were taken as follows:

Injection 1 (Day 1): immediately before (predose); at 8, 24, 48, 72, and 96 hours after the injection; and on Days 8, 11, 15, and 22 at the same time of the day as the injection.
Injection 2 (Day 29): immediately before (predose); 7 and 14 days after the injection (i.e., Days 36 and 43) at the same time of the day as the previous injection.
Injection 3 (Day 57): immediately before (predose); 7 and 14 days after the injection (i.e., Days 64 and 71) at the same time of the day as the previous injection.
Injection 4 (Day 85): immediately before (predose); at 8, 24, 48, 72, and 96 hours after the injection; and on Days 92, 95, 99, 106, 113, 141, and 169 at the same time of the day as the previous injection.

Descriptive statistics for plasma concentrations at each sampling time point and for all pharmacokinetic parameters; graphical exploration of steady-state dose-proportionality and of the correlation between the subject's genotype for CYP2D6 and the pharmacokinetic parameters after the last i.m. injection were presented.

Results:

Plasma concentrations of paliperidone palmitate were below the lower limit of quantification in most samples. It could be determined in a few samples only; the highest measured value was 1.58 ng/mL (dose corrected).

All subjects had detectable plasma levels of paliperidone within 8 hours after the first i.m. administration of paliperidone palmitate. No major differences between formulations were seen in the time to reach peak plasma concentrations (Cmax) after the first i.m. injection. After the last injection, Cmax was reached later with the F11 formulation, for both dose groups.

The pharmacokinetic parameters of paliperidone after the first and the last injection with paliperidone palmitate are summarized in the table below.

	n	mean ± SD	median	min - max
50 mg-eq. F4/F11 group			First injection F4	
C_{max}, ng/mL	15	10.9 ± 7.1	8.51	2.93 - 28.6
t_{max}, days	15	12.5 ± 8.3	10.0	3.0 - 28.0
$t_{1/2}$, days	10	30.5 ± 17.4	28.0	7.4 - 64.0
AUC_{28d}, ng.h/mL	15	5498 ± 3668	4650	1514 - 14911
50 mg-eq. F11/F4 group			First injection F11	
C_{max}, ng/mL	15	9.31 ± 6.33	7.49	2.20 - 27.5
t_{max}, days	15	14.0 ± 8.5	10.1	2.0 - 28.0
$t_{1/2}$, days	9	16.9 ± 9.7	13.9	6.5 - 34.3
AUC_{28d}, ng.h/mL	15	4161 ± 2802	3325	1111 - 11840
150 mg-eq. F4/F11 group			First injection F4	
C_{max}, ng/mL	15	26.6 ± 10.0	23.7	14.9 - 47.6
t_{max}, days	15	17.5 ± 8.1	14.2	7.0 - 28.0
$t_{1/2}$, days	6	-	-	6.0 - 53.2
AUC_{28d}, ng.h/mL	15	13101 ± 5145	11827	7186 - 25120
150 mg-eq. F11/F4 group			First injection F11	
C_{max}, ng/mL	15	26.7 ± 19.5	18.5	10.1 - 75.5
t_{max}, days	15	16.4 ± 9.2	21.0	2.0 - 28.0
$t_{1/2}$, days	6	-	-	7.5 - 83.2
AUC_{28d}, ng.h/mL	15	12180 ± 7096	10310	5833 - 31467
50 mg-eq. F4/F11 group			Last injection F11	
C_{max}, ng/mL	15	23.3 ± 14.4	21.1	6.79 - 66.3
t_{max}, days	15	9.6 ± 9.2	7.0	0.3 - 28.1
$t_{1/2}$, days	13	43.1 ± 31.0	26.3	13.2 - 123
AUC_{28d}, ng.h/mL	15	10732 ± 4230	10942	3227 - 17664
$C_{ss,av}$ ng/mL	15	16.0 ± 16.3	16.3	4.80 - 26.3
FI %	15	77.6 ± 78.3	58.6	25.3 - 354
Peak to trough ratio	15	230 ± 155	183	123 - 771
50 mg-eq. F11/F4 group			Last injection F4	
C_{max}, ng/mL	15	27.7 ± 21.9	25.3	7.79 - 96.7
t_{max}, days	15	7.8 ± 5.7	7.1	1.0 - 21.0
$t_{1/2}$, days	9	42.5 ± 20.5	38.5	18.7 - 84.4
AUC_{28d}, ng.h/mL	15	11275 ± 5008	11285	4138 - 21680
$C_{ss,av}$ ng/mL	15	16.8 ± 7.5	16.8	6.16 - 32.3
FI %	15	83.4 ± 66.2	69.0	22.0 - 231
Peak to trough ratio	15	251 ± 150	173	121 - 626
150 mg-eq. F4/F11 group			Last injection F11	
C_{max}, ng/mL	15	58.7 ± 22.4	56.5	31.4 - 97.9
t_{max}, days	15	19.9 ± 22.9	10.1	2.0 - 84.2
$t_{1/2}$, days	13	44.9 ± 29.5	38.2	18.5 - 136
AUC_{28d}, ng.h/mL	15	30455 ± 11619	29366	16064 - 50438
$C_{ss,av}$ ng/mL	15	45.3 ± 17.3	43.7	23.9 - 75.1
FI %	15	61.4 ± 28.9	56.3	23.3 - 125
Peak to trough ratio	15	197 ± 71	190	126 - 427
150 mg-eq. F11/F4 group			Last injection F4	
C_{max}, ng/mL	15	63.0 ± 23.9	57.6	35.0 - 113
t_{max}, days	15	13.4 ± 14.8	7.1	2.0 - 56.1
$t_{1/2}$, days	14	49.5 ± 26.9	43.3	13.8 - 105
AUC_{28d}, ng.h/mL	15	32129 ± 9989	29276	18959 - 49691
$C_{ss,av}$ ng/mL	15	47.8 ± 14.9	43.6	28.2 - 73.9
FI %	15	58.1 ± 27.5	53.9	14.9 - 109
Peak to trough ratio	15	194 ± 65	177	114 - 347

Both formulations had comparable Cmax after the first i.m. injection with 50 mg-eq. paliperidone. For the 150 mg-eq. dose group, mean Cmax values were comparable for both formulations, but median values were slightly lower with the F11 formulation than with the F4 formulation. After the last i.m. injection with 50 mg-eq. paliperidone, mean and median Cmax values for the F11 formulation were slightly lower than for the F4 formulation. For the 150 mg-eq. dose group, median Cmax values were comparable for both formulations.

AUC28d values were comparable between formulations for both dose groups and both the first and the last injection, except for the first injection with 50 mg-eq. paliperidone,

where exposure after injection with the F11 formulation was slightly lower when compared to the F4 formulation.

The doses and formulations tested were dose-proportional.

There was no indication of a relationship between paliperidone pharmacokinetic parameters and metabolizer status.

Comments

1. The study showed comparable Cmax and AUC between two formulations to support further formulation development.

6. Single dose study in Japanese (R092670-JPN-1)

Study Title: A single dose study of JNS010 in patients with schizophrenia

Objective: To assess the pharmacokinetic characteristics and safety of JNS010 (25 mg eq., 50 mg eq., 150 mg eq.) in patients with schizophrenia in a single dose, open-label study.

Investigators and study sites: (b) (4) and others. (b) (4) and others - a total of 9 medical institutions.

Trail period: November 9, 2005 (Date of obtaining consent from the first subject) to August 14, 2006 (Date of completing observation and examination of the last subject)

Subjects: 24 subjects (8 subjects in each group) were planned. 26 patients at least 20 years of age and younger than 65 years of age were enrolled, treated and included in pharmacokinetic analysis.

Study Design: This study was designed as a multicenter, single dose, open-label, parallel-group study aimed at assessing the pharmacokinetic characteristics and safety of JNS010 (25 mg eq., 50 mg eq., 150 mg eq.) in patients with schizophrenia. The patients were randomly assigned to any of the groups by the registration center.

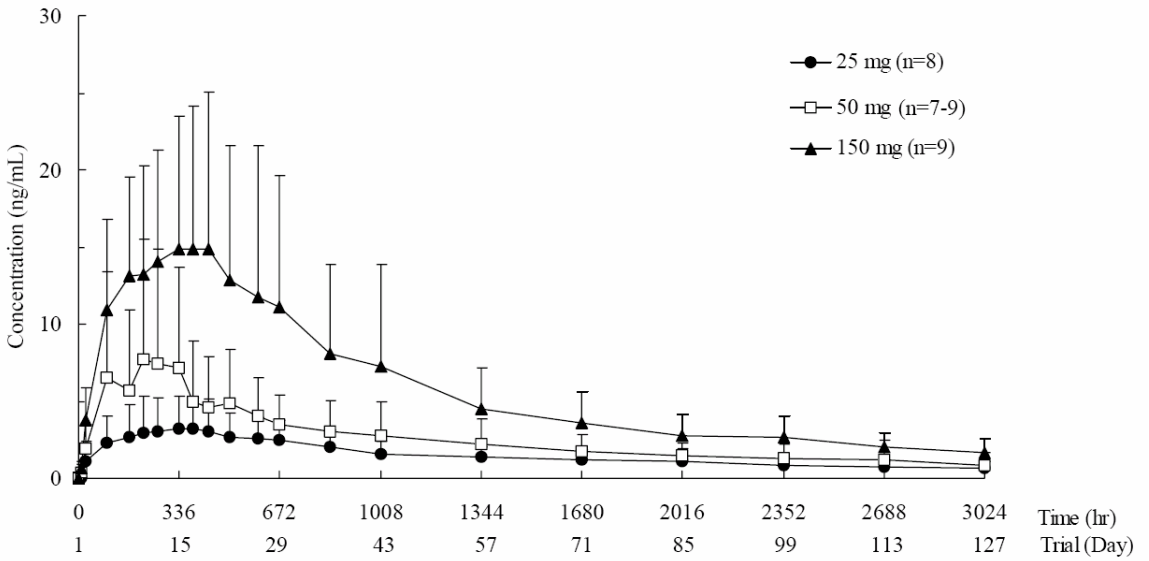
Patients assigned to Group A (25 mg eq. group) received a single dose of JNS010 25 mg eq. in the gluteal muscle, while Group B (50 mg eq. group) and Group C (150 mg eq. group) received 50 mg eq. and 150 mg eq., respectively, in the same manner as Group A. During the observation period, blood sampling for determination of plasma drug concentrations and evaluation of safety endpoints were conducted. Efficacy endpoints were also assessed for generation of reference data.

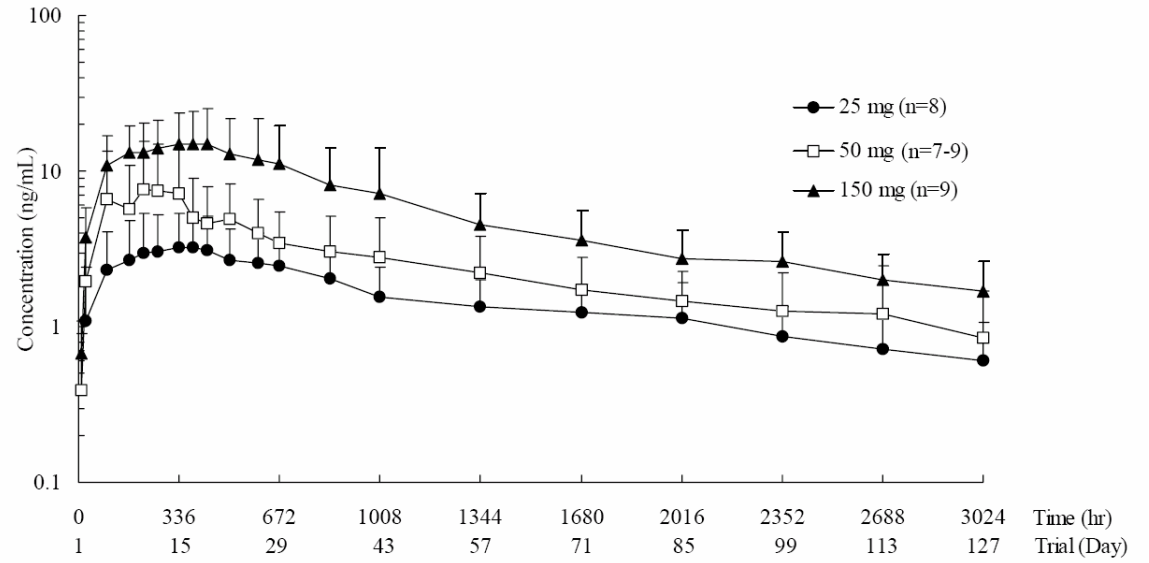
Measurement values of plasma concentrations of paliperidone palmitate as well as paliperidone and its enantiomer (R078543 and R078544) concentrations were analyzed in each subject. Blood samples were collected before the study drug treatment, 8 hours after the study drug treatment, 24 hours after the study drug treatment (Day 2), and Days 5, 8, l0, 12, 15, 17, 19, 22, 26, 29, 36, 43, 57, 71, 85, 99, 113, and 127. If a patient was withdrawn from the study after the study drug treatment, blood samples were collected where possible. On Day 3 and after, the samples were collected at the same hour as the treatment time on Day 1 where possible.

All of the analyses were conducted with each group serving as a unit. Changes in plasma drug concentration from plasma drug concentrations in each subject, descriptive statistics (mean, standard deviation, median, minimum, maximum, etc.) at each timepoint of blood sampling were calculated.

Results:

Figure and table below show changes in mean plasma concentration and pharmacokinetic parameters of paliperidone in schizophrenia subjects and mean values at each dose when JNS010 25 mg eq., 50 mg eq. or 150 mg eq. was intramuscularly injected once in patients.



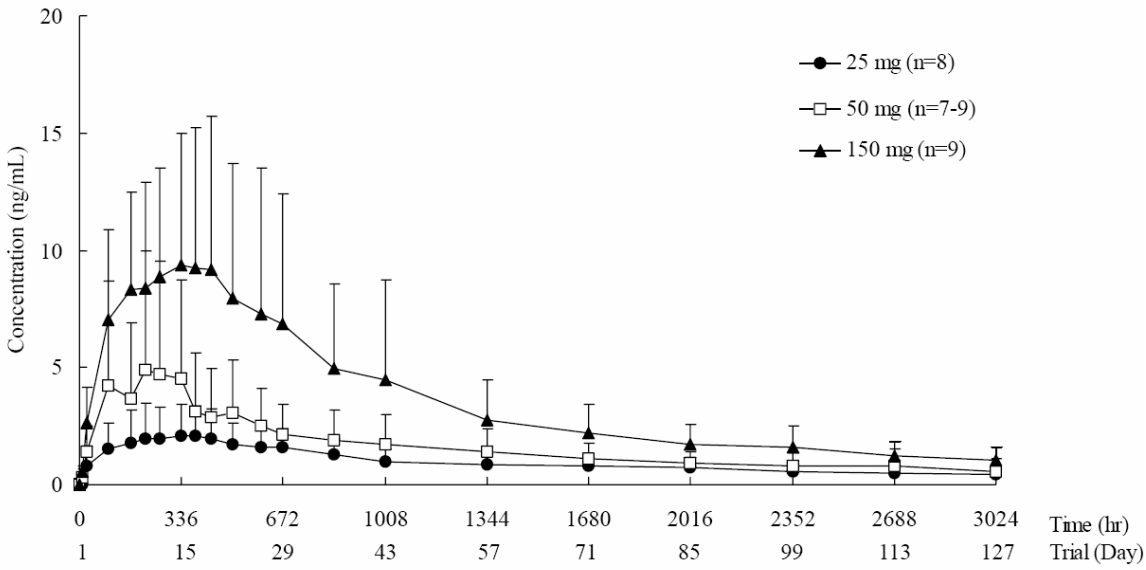


JNS010 25 mg eq., paliperidone		n	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	8	3.678	±	2.262	3.29	0.611	7.69
t_{max}	(hr)	8	360.0	±	162.3	384	96	600
	(day)	8	15.00	±	6.76	16.0	4.0	25.0
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	8	4633.51	±	2385.51	4401.3	215.6	7700.5
AUC	(ng·hr/mL)	8	5713.18	±	2829.37	6110.4	290.6	9039.1
$t_{1/2}$	(hr)	8	1131.52	±	1123.38	724.0	251.1	3801.8
	(day)	8	47.15	±	46.81	30.2	10.5	158.4

JNS010 50 mg eq., paliperidone		n	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	8	7.940	±	6.637	7.19	2.60	23.0
t_{max}	(hr)	8	375.5	±	288.6	264	96	1012
	(day)	8	15.64	±	12.02	11.0	4.0	42.2
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	8	7353.23	±	3750.68	8270.4	3082.8	13189.3
AUC	(ng·hr/mL)	8	9197.76	±	4764.32	10108.0	3488.2	14532.9
$t_{1/2}$	(hr)	8	1073.08	±	518.79	1085.1	324.4	1932.9
	(day)	8	44.71	±	21.62	45.2	13.5	80.5

JNS010 150 mg eq., paliperidone		n	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	9	17.23	±	9.95	18.7	4.51	37.4
t_{max}	(hr)	9	357.4	±	175.3	432	96	672
	(day)	9	14.89	±	7.31	18.0	4.0	28.0
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	9	17764.24	±	9538.43	17228.0	5607.3	35604.6
AUC	(ng·hr/mL)	9	20860.91	±	9959.70	19447.5	6630.2	36206.6
$t_{1/2}$	(hr)	9	1192.02	±	543.18	1080.8	491.9	2227.7
	(day)	9	49.67	±	22.63	45.0	20.5	92.8

Figure and table below show changes in mean plasma concentration and pharmacokinetic parameters of R078543 in schizophrenia subjects and mean values at each dose when JNS010 25 mg eq., 50 mg eq. or 150 mg eq. was intramuscularly injected once in patients.


20
15
10
5
0
Concentration (ng/mL)
25 mg (n=8)
50 mg (n=7-9)
150 mg (n=9)
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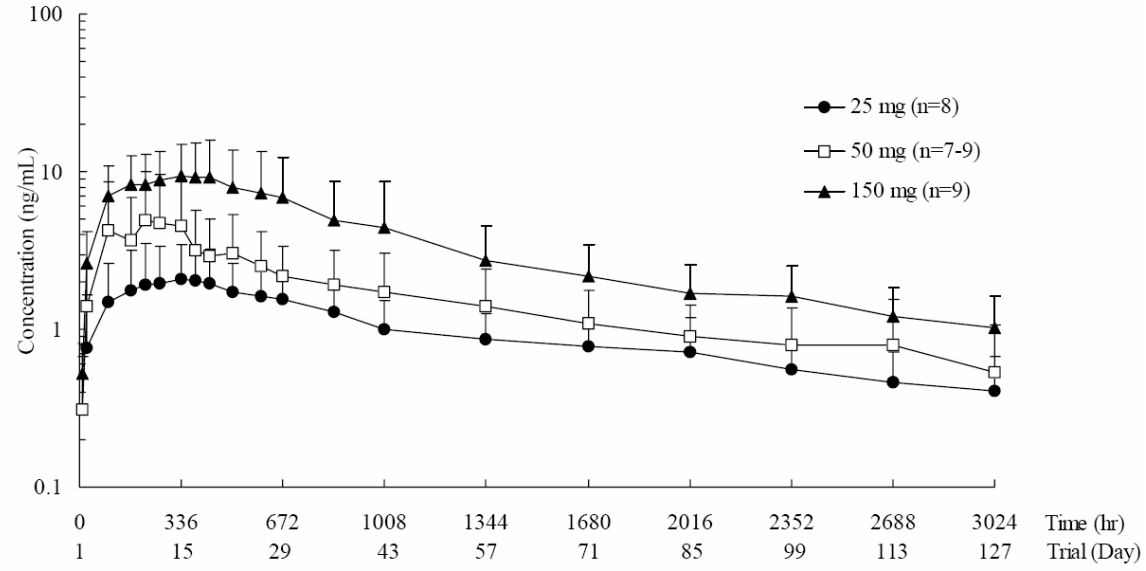
Time (hr)
1 15 29 43 57 71 85 99 113 127
Trial (Day)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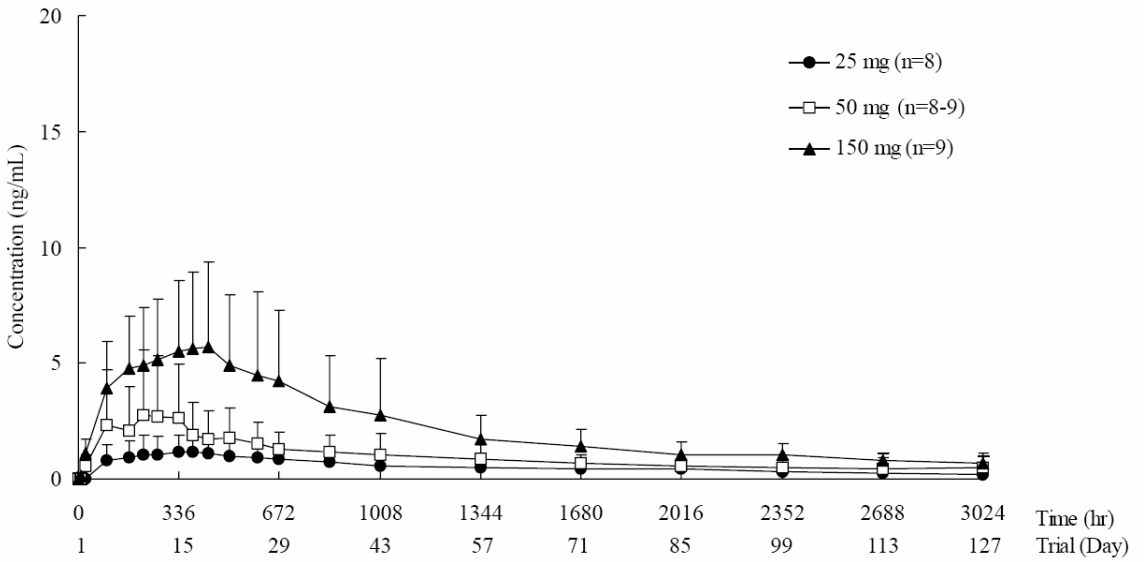
10
1
0.1
Concentration (ng/mL)
25 mg (n=8)
50 mg (n=7-9)
150 mg (n=9)
0 336 672 1008 1344 1680 2016 2352 2688 3024
Time (hr)
1 15 29 43 57 71 85 99 113 127
Trial (Day)

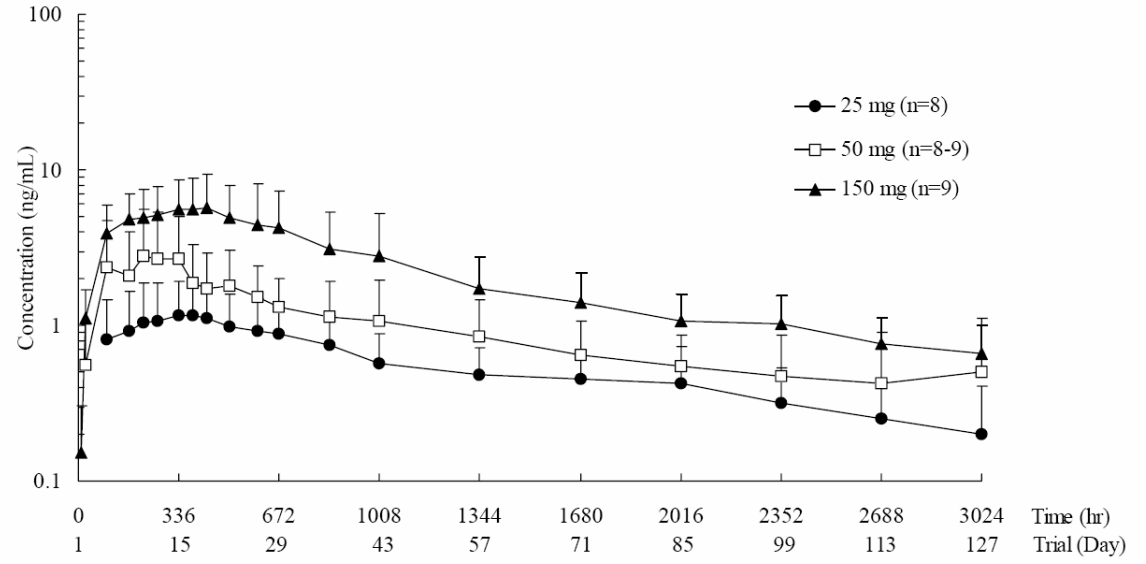
JNS010 25 mg eq., R078543		n	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	8	2.384	±	1.500	2.13	0.365	5.05
t_{max}	(hr)	8	354.0	±	167.1	384	96	600
	(day)	8	14.75	±	6.96	16.0	4.0	25.0
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	8	2965.72	±	1500.53	2788.3	176.6	4968.9
AUC	(ng·hr/mL)	8	3622.93	±	1691.17	3851.4	263.8	5704.2
$t_{1/2}$	(hr)	8	1108.50	±	783.92	864.9	286.7	2790.5
	(day)	8	46.19	±	32.66	36.0	11.9	116.3

JNS010 50 mg eq., R078543		n	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	8	5.065	±	4.418	4.49	1.60	15.2
t_{max}	(hr)	8	369.5	±	291.7	264	96	1012
	(day)	8	15.39	±	12.16	11.0	4.0	42.2
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	8	4641.82	±	2431.87	5138.9	2000.7	8615.6
AUC	(ng·hr/mL)	8	5786.80	±	3035.47	6266.3	2458.1	9240.0
$t_{1/2}$	(hr)	8	1087.11	±	471.61	1059.2	466.9	1875.7
	(day)	8	45.30	±	19.65	44.1	19.5	78.2

JNS010 150 mg eq., R078543		n	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	9	10.93	±	6.43	12.5	2.93	24.1
t_{max}	(hr)	9	352.1	±	173.5	384	96	672
	(day)	9	14.67	±	7.23	16.0	4.0	28.0
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	9	11026.03	±	6105.50	10535.0	3595.0	22903.4
AUC	(ng·hr/mL)	9	12788.90	±	6367.13	11686.5	4241.8	23139.4
$t_{1/2}$	(hr)	9	1138.73	±	536.01	1031.3	363.8	2143.0
	(day)	9	47.45	±	22.33	43.0	15.2	89.3

Figure and table below show changes in mean plasma concentration and pharmacokinetic parameters of R078544 in schizophrenia subjects and mean values at each dose when JNS010 25 mg eq., 50 mg eq. or 150 mg eq. was intramuscularly injected once in patients.


20
15
10
5
0
Concentration (ng/mL)
25 mg (n=8)
50 mg (n=8-9)
150 mg (n=9)
0
336
672
1008
1344
1680
2016
2352
2688
3024
Time (hr)
1
15
29
43
57
71
85
99
113
127
Trial (Day)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10
1
0.1
Concentration (ng/mL)
25 mg (n=8)
50 mg (n=8-9)
150 mg (n=9)
0
336
672
1008
1344
1680
2016
2352
2688
3024
Time (hr)
1
15
29
43
57
71
85
99
113
127
Trial (Day)

JNS010 25 mg eq., R078544		n	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	8	1.305	±	0.768	1.19	0.246	2.64
t_{max}	(hr)	8	393.0	±	172.6	408	96	600
	(day)	8	16.38	±	7.19	17.0	4.0	25.0
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	8	1658.63	±	893.02	1618.7	30.1	2702.5
AUC	(ng·hr/mL)	7	2467.17	±	816.37	2515.3	1336.3	3418.6
$t_{1/2}$	(hr)	7	1483.77	±	1697.83	805.8	576.5	5271.9
	(day)	7	61.82	±	70.74	33.6	24.0	219.7

JNS010 50 mg eq., R078544		N	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	8	2.886	±	2.222	2.52	0.996	7.78
t_{max}	(hr)	8	375.5	±	288.6	264	96	1012
	(day)	8	15.64	±	12.02	11.0	4.0	42.2
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	8	2754.16	±	1390.36	3131.5	997.6	4529.3
AUC	(ng·hr/mL)	8	3769.48	±	2235.44	3934.0	1239.7	7644.8
$t_{1/2}$	(hr)	8	1295.88	±	635.08	1184.7	454.2	2043.2
	(day)	8	54.00	±	26.46	49.4	18.9	85.1

JNS010 150 mg eq., R078544		N	Mean	±	SD	Median	Min	Max
C_{max}	(ng/mL)	9	6.371	±	3.585	6.78	1.58	13.3
t_{max}	(hr)	9	370.7	±	149.9	384	168	672
	(day)	9	15.44	±	6.25	16.0	7.0	28.0
$AUC_{(0\rightarrow t)}$	(ng·hr/mL)	9	6738.21	±	3470.95	6693.0	2012.3	12701.2
AUC	(ng·hr/mL)	9	7956.65	±	3592.44	7614.8	2387.8	12911.8
$t_{1/2}$	(hr)	9	1212.20	±	577.43	1091.7	481.0	2351.0
	(day)	9	50.51	±	24.06	45.5	20.0	98.0

Comments:

1. Although this study did not specify the formulation used, it did support the following points.

    - Plasma concentrations of paliperidone palmitate remained to be lower than the lower limit of quantitation at all timepoints of measurement.
    - Plasma concentrations of paliperidone were highly variable among subjects. Concentrations of its enantiomers R078543 and R078544 were also highly variable among subjects.
    - Plasma concentrations of R078543 and R078544 reached the Cmax at 14.67-15.39 days and 15.44-16.38 days (tmax) post-dosing and declined with t1/2 of 45.30-47.45 days and 50.51-61.82 days. The values of these parameters were similar at dose levels examined.

7. Multiple dose study comparing injection sites using F013 (R092670-PSY-1001)

Study Title: Open-Label, Parallel, Randomized, Multiple-Dose Pharmacokinetic Study of Paliperidone after Intramuscular Injection of Paliperidone Palmitate in the Deltoid or Gluteal Muscle in Subjects with Schizophrenia

Objective: The primary objective of this study was to characterize and compare the pharmacokinetics of paliperidone at steady state following multiple intramuscular (i.m.) injections of paliperidone palmitate in the deltoid and gluteal muscle. In addition, the safety and tolerability of paliperidone palmitate i.m. injections were evaluated.

Investigators and study sites: (b) (4)

Trail period: Clinical Conduct: July 24, 2005 –March 29, 2006. Sample Analysis: February 20, 2006 –April 18, 2006.

Subjects: Planned: 40 subjects. Analyzed: 49 subjects. Subjects were men and women, aged 22 to 60 years, inclusive, with a diagnosis of schizophrenia of any subtype.

Study Design: This was a single-country, multiple-dose, open-label, randomized, parallel-group study in subjects with schizophrenia. The study had a screening period (within 21 days before the first i.m. injection of the study drug), an open-label treatment phase during which subjects received a total of 4 i.m. injections of paliperidone palmitate equivalent to 100 mg paliperidone (i.e., paliperidone palmitate 100 mg eq.) on Days 1, 8, 36, and 64, and an end-of-study evaluation period upon completion of the treatment period on Day 176 (or early withdrawal).

Four i.m. injections of paliperidone palmitate 100 mg eq. long-acting formulation were administered into the gluteal or deltoid muscle on Day 1, Day 8, Day 36, and Day 64.

Subjects without source documentation of previous treatment with risperidone, paliperidone, paliperidone palmitate, or injectable Risperdal CONSTA™ received 4 daily doses of 3 mg/day extended-release (ER) paliperidone to evaluate their ability to tolerate the drug. This 4-day testing period was completed at or before Day –8 (i.e., at least 8 full days before the first i.m. injection of paliperidone palmitate).

Subjects were randomly assigned to 1 of 2 treatment groups and received paliperidone palmitate 100 mg eq. injections in either the gluteal or deltoid muscle.

Four-milliliter venous blood samples to obtain approximately 2 mL of plasma were collected via venipuncture to determine plasma concentrations of paliperidone enantiomers at the following time points: predose and 8 hours postdose on Day 1; on Days 2, 4, and 6; predose on Day 8; on Days 15, 18, 20, 22, and 29; predose on Day 36;

on Days 43, 46, and 50; predose and 8 hours postdose on Day 64; and on Days 65, 66, 67, 69, 71, 74, 76, 78, 85, 92, 99, 106, 120, 134, 148, 162, and 176.

Additional 4-mL blood samples were collected for the determination of paliperidone palmitate plasma concentrations at the following time points: predose and 8 hours postdose on Day 1; on Days 2, 4, and 6; predose on Day 8; on Day 15; predose on Day 36; on Day 43; predose and 8 hours postdose on Day 64; and on Days 65, 66, 67, 69, 71, 74, 76, and 78.

The total paliperidone concentration was calculated as the sum of both enantiomers. Based on the individual plasma concentration-time data, the following PK parameters were estimated for paliperidone and its enantiomers: Cpredose, Cmin, Cmax, tmax, λz, t1/2, AUClast, AUCt, AUC∞, Cavg,ss, FI, CL/F, accumulation ratio and peak to trough ratio.

Descriptive statistics were calculated by injection site (gluteal or deltoid) for the plasma concentrations and PK parameters of paliperidone and its enantiomers. To compare the deltoid and gluteal group, an analysis of variance (ANOVA) was performed to calculate the mean treatment ratios (fourth i.m. injection/second i.m. injection for AUCt and Cmax in the deltoid and gluteal muscle) and their 90% confidence intervals. A general linear model with the factor of injection site was used. The least square means and the mean squared error from the ANOVA model was used for 90% confidence interval calculations.

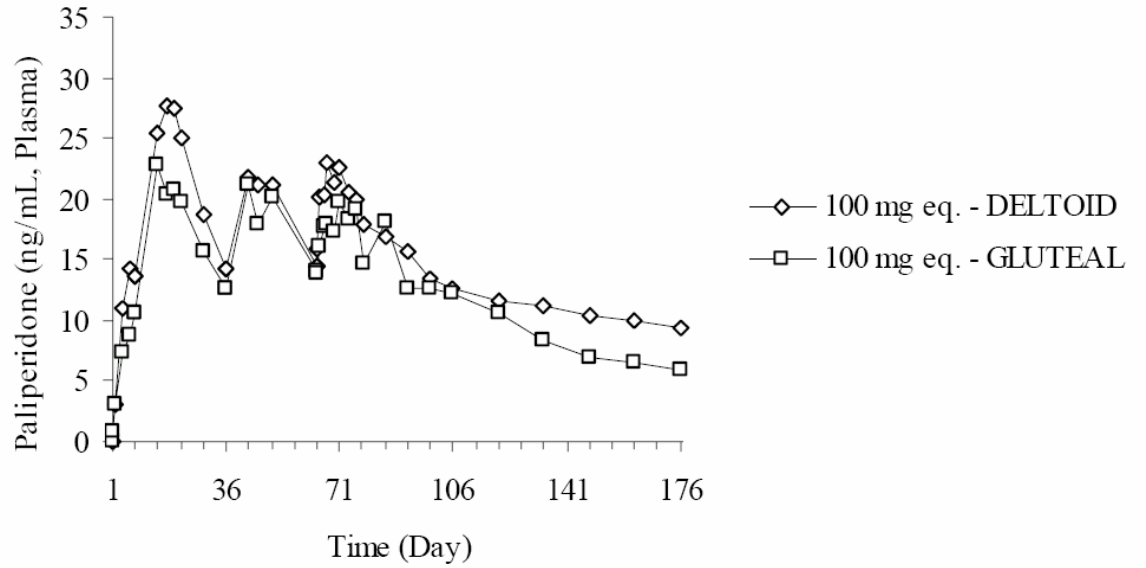
To compare the fourth i.m. injection with the second i.m. injection, an analysis of variance (ANOVA) was performed to calculate the mean treatment ratios (deltoid/gluteal for AUCt and Cmax after the fourth administered dose) and their 90% confidence intervals. The least square means and the mean squared error from the ANOVA model was used for 90% confidence interval calculations.

Results:

Enantiomers of paliperidone (R078543 and R078544) and paliperidone palmitate (R092670) plasma levels were determined using LC-MS/MS method. The following table shows the assay performance.

Species	LLOQ	Range	QC	samples	Calibration	standards
	(ng/mL)	(ng/mL)	Accuracy (%)	Precision (CV%)	Accuracy (%)	Precision (CV%)
R092670	0.20	0.2-100	-12.4 to 2.2	3.2 to 11.6	-1.2 to 1.2	1.4 to 4.8
R078543	0.20	0.2-100	-3.2 to 0.4	2.1 to 7.4	-1.0 to 1.5	1.8 to 3.4
R078544	0.20	0.2-100	-4.0 to 0.9	2.5 to 5.8	-1.0 to 1.2	1.7 to 3.6

The median concentration-time profile of paliperidone, after i.m. administration of 100 mg eq. paliperidone palmitate in the gluteal muscle, was consistently lower compared to i.m. injection in the deltoid muscle as shown in the following figure.

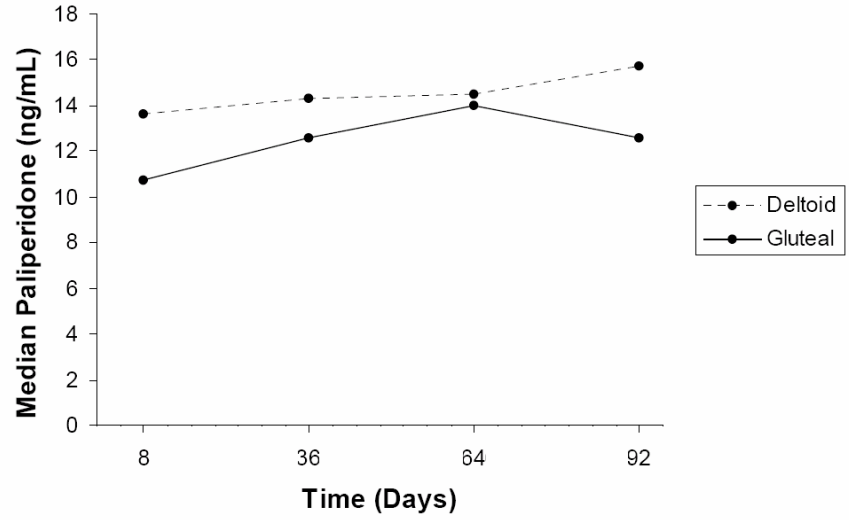


A summary of the PK parameters of paliperidone after i.m administration of paliperidone palmitate (on Days 1, 8, 36 and 64), in the deltoid and gluteal muscle is given in the following Table.

	Second i.m. injection				Fourth i.m. injection			
	Deltoid		Gluteal		Deltoid		Gluteal	
Parameter	n	Median (min - max)	n	Median (min - max)	n	Median (min - max)	n	Median (min - max)
t_{max} (days)	22	9.95 (6.94 – 20.86)	24	10.02 (6.94 – 21.08)	21	4.99 (1.13 – 13.96)	24	6.54 (0.98 – 20.12)
C_{max} (ng/mL)	22	31.3 (15.8 – 67.4)	24	24.1 (9.10 – 50.2)	21	23.7 (8.27 – 71.6)	24	22.3 (6.44 – 56.1)
AUC_{τ} (ng.h/mL)	22	14728 (8253 – 26453)	24	12108 (4736 – 24754)	20	12946 (4287 – 27621)	23	11021 (3198 – 26749)
C_{avg} (ng/mL)	22	21.9 (12.3 – 39.5)	24	18.0 (7.06 – 36.8)	20	19.2 (6.38 – 42.6)	23	16.4 (4.76 – 41.3)
FI (%)	22	88.6 (57.8 – 138)	24	94.8 (53.2 – 160)	20	71.9 (32.6 – 177)	23	56.2 (40.7 – 107)

Note: Paliperidone Palmitate was administered in either the deltoid or gluteal muscle.

The median paliperidone predose plasma concentration on Days 8, 36, and 64 and the plasma concentration on Day 92 are graphically displayed in the following Figure.



A summary of the comparison of the geometric mean exposure parameters (Cmax and AUCt) of paliperidone after the fourth i.m. injection between deltoid and gluteal, performed on log-transformed data, is shown in the following Table.

Parameter	Estimated Ratio (%)[a] (Deltoid (n=19)/Gluteal (n=23))	90% CI
AUC_{τ} (ng.h/mL)	120.00	(93.09-154.69)
C_{max} (ng/mL)	130.34	(100.56-168.93)

[a] Data analyzed on log scale, but statistics transformed back to original scale .
CI: Confidence interval

The relative exposure after the fourth injection was lower than after the second injection in the deltoid muscle (14% for Cmax and 9% for AUCt) and the gluteal muscle (15% for Cmax and 6% for AUCt) as shown in the following Table.

Treatment Group	Parameter	Estimated Ratio (%)[a] Fourth/Second	90% CI
100 mg eq. DELTOID (n=18)	AUC_{τ} (ng.h/mL)	91.04	(79.90-103.73)
	C_{max} (ng/mL)	85.68	(72.78-100.88)
100 mg eq. GLUTEAL (n=22)	AUC_{τ} (ng.h/mL)	93.72	(83.78-104.85)
	C_{max} (ng/mL)	84.91	(75.10-96.01)

[a] Data analyzed on log scale, but statistics transformed back to original scale.
CI: Confidence interval

Comments:

1. The median concentrations of paliperidone, after i.m. administration of paliperidone palmitate in the deltoid muscle, were consistently higher compared to i.m. injection in the gluteal muscle. The highest median peak paliperidone plasma concentrations were obtained after the second i.m. injection, i.e. 31.3 ng/mL for the deltoid and 24.1 ng/mL for the gluteal. The median peak paliperidone plasma concentration after the fourth i.m. injection was 23.7 and 22.3 ng/mL for the deltoid and gluteal, respectively. The median fluctuation index after the fourth i.m injection was higher for the deltoid compared to the gluteal (71.9% vs. 56.2%) with a larger variability in the deltoid compared to the gluteal. After the fourth i.m. injection, the relative exposure of paliperidone was approximately 30% and 20% higher for Cmax and AUCt, respectively, in the deltoid muscle compared to the gluteal muscle.
2. Based upon the median paliperidone predose plasma concentrations, it appears that after 4 i.m. injections of paliperidone palmitate 100 mg eq. (this study), subjects were not completely at steady-state (reflected in the increase of the median predose concentrations after Day 8); Paliperidone reached maximum plasma concentrations 10 days after the second injection and 5 to 6 days after the fourth injection of paliperidone palmitate, independent of the injection site.

3. Only 3 of 49 subjects had detectable paliperidone palmitate concentrations at a limited number of time-points;

8. Multiple dose study comparing injection sites using F011 (R092670-USA-3)

Study Title: Pharmacokinetics, Tolerability, and Safety of Paliperidone after Repeated Intramuscular Injection of Paliperidone Palmitate (R092670) in the Arm or the Buttock of Subjects with Schizophrenia.

Objective: to compare the pharmacokinetics of paliperidone and its palmitate ester after intramuscular (i.m.) injection of paliperidone palmitate in 2 different injection sites, the deltoid (arm) and the gluteus (buttock). In addition, the safety and tolerability of paliperidone palmitate after i.m. deltoid or i.m. gluteal injections were evaluated. The relationship between genetic variability in the drug metabolizing enzymes CYP2D6, CYP3A4, and CYP3A5, and pharmacokinetic parameters were explored.

Investigators and study sites: (b) (4)

Trail period: Clinical Conduct: August 18, 2003 –May 3, 2004. Sample Analysis: March 15, 2004 –May 18, 2004.

Subjects: 72 planned, 83 analyzed and 79 completed. The subjects were male or female subjects aged 18 to 65 years, healthy based on a prestudy physical examination, electrocardiogram (ECG), and clinical laboratory evaluation and clinically stable, with diagnosis of schizophrenia of any subtype according to DSM-IV, body mass index between 15 and 35 kg/m^2; and a total Positive and Negative Syndrome Scale (PANSS) score of 90 or less.

Study Design: This was a repeated-dose, open-label, multicenter, parallel-group study in subjects with a DSM-IV (Diagnostic Statistical Manual of Mental Disorders Fourth Edition) axis I disorder of schizophrenia to compare the pharmacokinetics, safety, and tolerability of paliperidone palmitate 25 mg eq. or 150 mg eq. administered by deep i.m. deltoid injection or by deep i.m. gluteal injection.

A total of 72 subjects were to be enrolled in the study. After screening, all eligible subjects were exposed to oral risperidone for up to 3 days to confirm that the subjects developed no allergic reactions to risperidone, and to help the investigator to assign subjects to one of 2 fixed paliperidone palmitate treatment doses (25 mg eq. or 150 mg eq. paliperidone). After a washout of at least 14 days starting after the last oral risperidone intake, subjects received the first injection of paliperidone palmitate in the deltoid or gluteal muscle according to the randomization schedule. The 2 injections, separated by 1 week, alternated between the left and right side.

Blood sampling were collected as follows.

Injection 1 (Day 1): immediately before (predose) and at 4, 8, 12, 24 hours (Day 2), 48 hours (Day 3), 72 hours (Day 4), and 96 hours (Day 5) after the first injection at the same time of the day as the i.m. injection.

Injection 2 (Day 8): immediately before (predose) and at 4, 8, 12, 24 (Day 9), 48 (Day 10), 72 (Day 11) and 96 hours (Day 12) after the second injection, and on Days 15, 18, 22, 29, 36, 43, 50, 57, and 64 of the study at the same time of the day as the i.m. injection.

The following pharmacokinetic parameters were estimated after the first dose: tmax1 and Cmax1. The following pharmacokinetic parameters were estimated after the second dose: t_{max2}, t_{last}, C_{max2}, C_{min2}, AUC_{0-36d}, AUC_{last}, AUC_{∞}, $\%AUC_{\infty,ex}$, t1/2, and λz. Descriptive statistics were calculated for the plasma concentrations and pharmacokinetic parameters of paliperidone for both dosing groups (paliperidone palmitate 25 mg eq. or 150 mg eq.) and injection sites (deltoid or gluteus).

To compare the gluteal group with the deltoid group, an analysis of variance (ANOVA) was performed to calculate the mean treatment ratios (deltoid/gluteal: Cmax2, AUC0-36d, AUClast, and AUC∞) and their 90% confidence limits at both dose levels (25 and 150 mg eq.). A general linear model with the factor of injection site was used. The least square means of each dose level within each group and the mean squared error from the ANOVA model was used for 90% confidence interval (CI) calculations. All information on dropouts was included in the analysis if their pharmacokinetic parameters were estimated. Tmax was compared across the 2 sites using descriptive statistics.

The dose proportionality of paliperidone palmitate 25 and 150 mg eq. was evaluated by plotting the dose-normalized parameters (Cmax2, AUC0-36d, and AUClast) versus dose.

Preferably on Day 1, or at any time thereafter, one blood sample (10 mL) was collected from subjects consenting to the genetic component of the trial. The impact of genetic variation of the CYP2D6, CYP3A4, and CYP3A5 genes on pharmacokinetics of paliperidone palmitate was examined graphically.

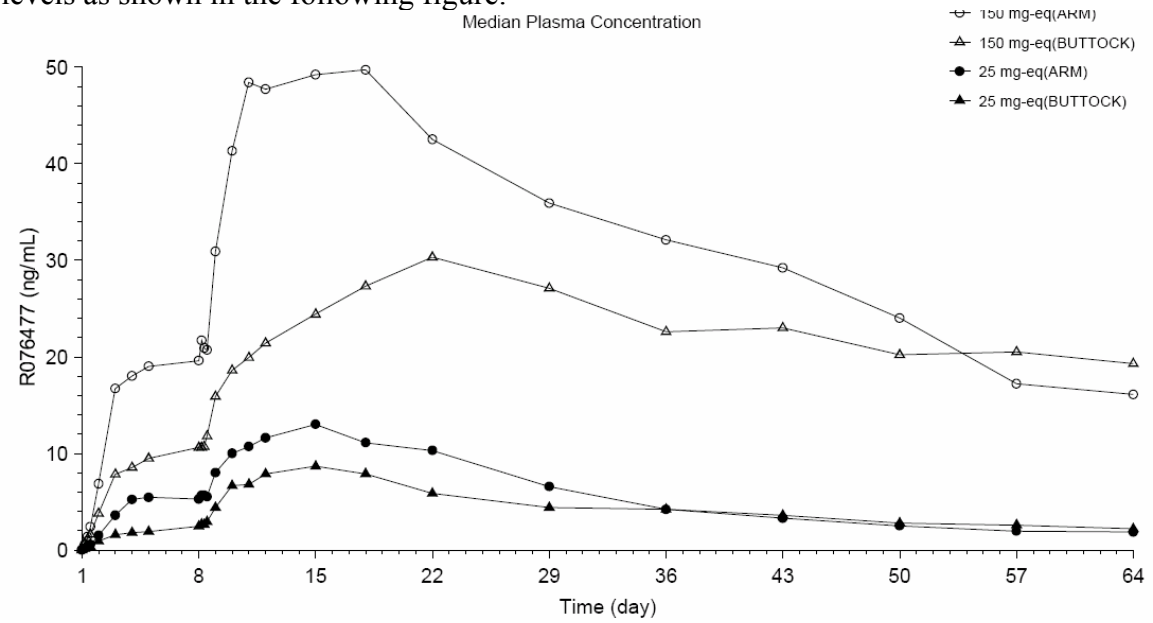
Results:

Paliperidone (R76477) and paliperidone palmitate (R92670) plasma levels were determined using LC-MS/MS method. The following table shows the assay performance.

Species	LLOQ	Range	QC	samples	Calibration	standards
	(ng/mL)	(ng/mL)	Accuracy (%)	Precision (CV%)	Accuracy (%)	Precision (CV%)
R092670	0.20	0.2-100	-5.7 to -7	3.1 to 4.0	-1.2 to 1.6	2.2 to 4.2
R076477	0.10	0.1-250	0.2 to 2.1	3.3 to 5.1	-2.5 to 4.0	1.7 to 5.1

The median plasma concentration-time profiles of paliperidone, after i.m. administration of paliperidone palmitate, were lower for both dosing groups when injected in the gluteal muscle compared to the deltoid muscle. Paliperidone plasma concentrations reached peak levels for the 25 mg eq. and 150 mg eq. dose group at 6.50 and 10.0 days, respectively.

The obtained median Cmax, after the second dose, for the paliperidone palmitate 25 mg eq. was 10.1 ng/mL for the gluteus and 15.3 ng/mL for the deltoid. For the 150 mg eq. dose group, median Cmax values were 41.0 ng/mL for the gluteus and 66.0 ng/mL for the deltoid. The median plasma exposure (AUC0-36d) after the first and second dose at both dose levels was also lower for i.m. gluteal injections compared to i.m. deltoid injections. The total exposure (AUC∞) was similar for the deltoid and gluteal injections at both dose levels as shown in the following figure.



Pseudo steady state was achieved after the second dose for the 25 mg eq. dose group. This was not the case for the 150 mg eq. dose group, i.e., the median paliperidone plasma concentrations on Day 36, the day of the next i.m. injection if an every-4-hour injection interval would be applied, were higher than those observed on Day 8 (predose to the second injection).

A summary of the pharmacokinetic parameters of paliperidone after i.m. administration of paliperidone palmitate, in the deltoid and gluteal muscle (on Days 1 and 8) is given in Table below. The pharmacokinetic parameters were normalized to 50 mg eq. (2 doses of 25 mg eq.) or 300 mg eq. (2 doses of 150 mg eq.) for the actual dose administered.

Pharmacokinetic Parameter[a]	n	mean ± SD	%CV	median	min - max	n	mean ± SD	%CV	median	min - max
25 mg eq. dose group			Deltoid injection					Gluteal injection		
C_{max2}[b], ng/mL	18	14.8 ± 5.08	34.4	15.3	6.27 - 25.7	21	10.7 ± 5.52	51.7	10.1	2.29 -21.9
t_{max2}[b], days	18	6.36 ± 3.60	56.5	6.05	3.00 - 14.16	21	9.73 ± 8.48	87.2	7.00	2.00 - 35.00
AUC_{0-36d}, ng.h/mL	18	7905 ± 3139	39.7	7709	3686 - 16147	21	5453 ± 2749	50.4	5255	1166 - 11672
AUC_{last}, ng.h/mL	18	10594 ± 4774	45.1	9676	5129 - 24329	21	8151 ± 3864	47.4	7092	1683 - 15560
AUC_{∞}[c], ng.h/mL	15	13116 ± 5602	42.7	11435	6196 - 28311	18	11226 ± 4448	39.6	11040	2447 - 17853
$t_{1/2}$[c], days	15	19.2 ± 6.8	35.4	18.9	8.1 – 30.8	18	28.5 ± 14.8	52.0	23.5	11.6 – 64.6
150 mg eq. dose group			Deltoid injection					Gluteal injection		
C_{max2}[b], ng/mL	19	65.8 ± 24.1	36.6	66.0	33.8 - 119	21	51.4 ± 30.0	58.4	41.0	19.9 - 117
t_{max2}[b], days	19	10.70 ± 8.07	75.4	10.00	0.00 - 28.00	21	18.85 ± 17.42	92.4	10.00	2.01 - 56.00
AUC_{0-36d}, ng.h/mL	19	34456 ± 12680	36.8	32444	17127 - 57605	22	24071 ± 13346	55.4	21007	8627 - 62040
AUC_{last}, ng.h/mL	18	50951 ± 19638	38.5	48102	22447 - 90945	21	41144 ± 15589	37.9	38099	13962 - 76629
AUC_{∞}[c], ng.h/mL	17	67061 ± 26518	39.5	63249	24548 - 112073	13	61437 ± 17656	28.7	54659	36733 - 91019
$t_{1/2}$[c], days	17	26.4 ± 8.9	33.6	23.5	13.7 – 43.3	13	29.0 ± 10.1	34.8	27.1	12.2 – 48.8

[a] Pharmacokinetic parameters were corrected for the actual dose administered and normalized to 2 times 25 or 2 times 150 mg eq., respectively.
[b] An i.m. dose was administered on Days 1 and 8, after which the pharmacokinetic profiles were determined. The time at which the maximum concentration (C_{max2}) is achieved after the second dose is reflected in t_{max2}.
[c] Interpret with caution because for some subjects $\%AUC_{ex}$ was higher than 20%.
Acronym: CV: coefficient of variance.

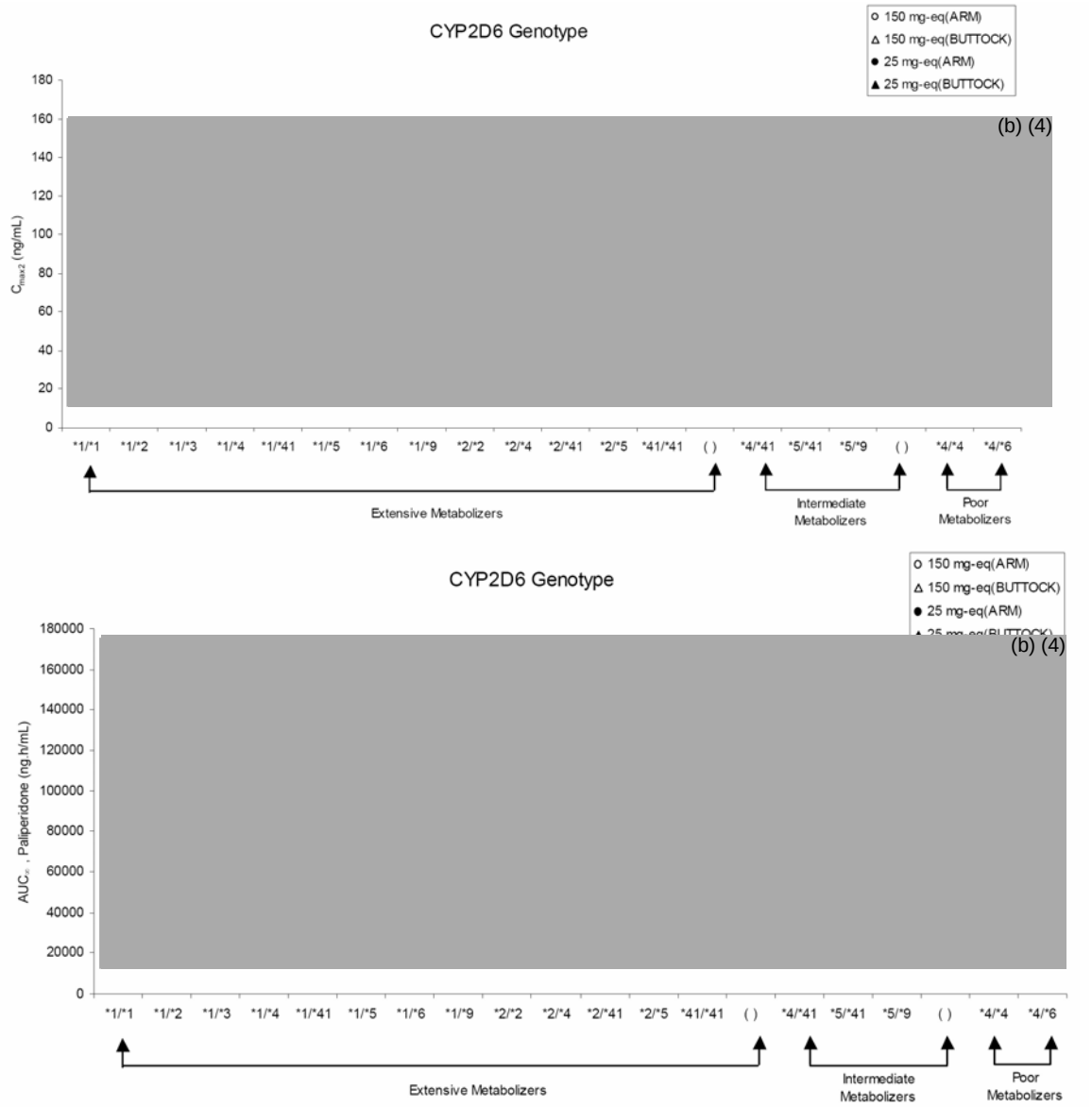
The treatment ratios of the dose adjusted AUC0-36d, AUC∞, AUClast, and Cmax2 did not fall within the equivalence range of 80-125%. The peak and AUC0-36d (relative bioavailability) was approximately 50% higher after injection in the deltoid compared to gluteal muscle. However, for the total estimated exposure, AUC∞, the difference is less between both injection sites as shown in the following table.

Pharmacokinetic Parameter[a,b]	Dose	Least square means				A/B, %	
		n	Deltoid (A)	n	Gluteal (B)	Ratio	90% CI
AUC_{0-36d}, ng.h/mL	25 mg eq.	18	7350	21	4788	153.53	(118.13; 199.54)
	150 mg eq.	19	32215	22	21219	151.82	(119.52; 192.85)
AUC_{∞}, ng.h/mL	25 mg eq.	15	12227	18	10139	120.60	(91.97; 158.14)
	150 mg eq.	17	61670	13	59142	104.27	(82.05; 132.52)
AUC_{last}, ng.h/mL	25 mg eq.	18	9755	21	7224	135.03	(104.01; 175.31)
	150 mg eq.	18	47195	21	38299	123.23	(98.85; 153.61)
C_{max2}, ng/mL	25 mg eq.	18	13.9	21	9.28	149.69	(114.87; 195.05)
	150 mg eq.	19	61.9	21	44.3	139.74	(108.75; 179.56)

[a] Data analyzed on log scale and statistics transformed back to original scale.
[b] Pharmacokinetic parameters were corrected for the actual dose administered and normalized to 2*25 or 2*150 mg eq.

Paliperidone palmitate was detected in 1.4% of the total number (1996) of analyzed blood samples. No further pharmacokinetic analysis was performed on these data.

No clear relationships were apparent between genetic variation in CYP2D6, CYP3A4, or CYP3A5 and the pharmacokinetic parameters of paliperidone. Due to the limited sample size, no firm conclusions can be drawn concerning the impact of genetic variation of these genes on the pharmacokinetics of paliperidone as shown in the following figure.



Subjects receiving paliperidone palmitate 25 mg eq. or 150 mg eq. i.m. gluteal injections had mean decreases (improvement) from baseline to end point in total PANSS of –0.90 and –3.62, respectively, while subjects receiving paliperidone palmitate 25 mg eq. or 150 mg eq. i.m. deltoid injections had mean increases (worsening) from baseline to end point in total PANSS of +3.28 and +2.72, respectively).

Common treatment-emergent adverse events occurring more frequently in subjects receiving paliperidone palmitate 150 mg eq. than in subjects receiving paliperidone palmitate 25 mg eq. regardless of injection site (deltoid or gluteus) were injection site pain (43% vs. 20%), somnolence (21% vs. 5%), insomnia (19% vs. 5%), tachycardia (12% vs. 5%), injection site reaction (10% vs. 2%), dyspepsia (10% vs. 5%), hyperkinesia (14% vs. 0%), and constipation (10% vs. 2%). Common treatment-emergent adverse events occurring more frequently in subjects receiving paliperidone palmitate 25 mg eq. than in subjects receiving paliperidone palmitate 150 mg eq. regardless of

injection site were weight increase (24% vs. 10%), headache (22% vs. 10%), postural hypotension (20% vs. 7%), and rhinitis (15% vs. 2%).

Common treatment-emergent adverse events occurring more frequently in subjects receiving gluteal injections than in subjects receiving deltoid injections regardless of dose (25 or 150 mg eq.) were weight increase (21% vs. 13%) and upper respiratory tract infection (14% vs. 5%). The common treatment-emergent adverse event occurring more frequently in subjects receiving deltoid injections than in subjects receiving gluteal injections regardless of dose (25 or 150 mg eq.) was injection site pain (41% vs. 23%).

Comments:
1. Steady state was not achieved after the second dose for the 150 mg eq. dose group, i.e., the median paliperidone plasma concentrations on Day 36, the day of the next i.m. injection if an every-4-hour injection interval would be applied, were higher than those observed on Day 8 (predose to the second injection).

9. Single dose pilot study formulation F1 (R092670-BEL-1)

Study Title: A single intramuscular injection of a 9-hydroxy-risperidone palmitate depot preparation to schizophrenic subjects: a pilot trial for pharmacokinetic and safety evaluation.

Objective: To evaluation of the safety and pharmacokinetics of an intrarnuscular injection of a 9-hydrox -risperidone almitate depot formulation..

Investigators and study sites: (b) (4)

Trail period: Clinical Conduct: November 27, 1996 to March 5, 1997.

Subjects: 9 subjects. The subjects were male or female subjects aged 18 to 65 years, with diagnosis of schizophrenia.

Study Design: This is a pilot, open label, single dose study. Samples (6 ml) will be taken just before and 1h, 2h, 4h, 8 h, 1 d, 2d, 4d, 7d, 10d, 14d, 21d, 28d, 35d, 42d, 49d and 56 days after the intramuscular injection. Additional monthly samples were taken from a selection of subjects up to 42 weeks until the levels dropped below the limit of quantification.

Results: The pharmacokinetic parameters are shown in the following table.

parameter	n	mean ± SD	median	min - max
C_{0h}, ng/ml	9	NQ	NQ	NQ - 0.26
C_{max}, ng/ml	9	5.37 ± 2.09	4.51	3.15 - 8.74
t_{max}, days	9	31.4 ± 12.2	28.0	16.0 - 56.0
AUC_{56days}, ng.h/ml	9	4227 ± 1168	4072	2523 - 5681
$t_{1/2\ term}$, days	4	74.8 ± 51.0	52.3	43.8 - 151
AUC_{∞}, ng.h/ml	4	11467 ± 3557	10858	7899 - 16252

Comments: The pilot formulation of R092670 did not exhibit an optimal in vivo release profile. The plasma level of R076477 remained low (median peak level: 4.51 ng/mL) and was measurable up to 28 weeks post-dose. The observed in vivo profile seems not optimal for future development, and further improvement of the R092670 depot formulation is warranted.

10. Single dose pilot study formulation F2 and F4 (R092670-BEL-2)

Study Title: Single-dose pharmacokinetics, tolerability and safety of two intramuscular depot formulations of 9-hydroxy-risperidone palmitate (R092670) in schizophrenic subjects.

Objective: To evaluate the pharmacokinetics, safety and tolerability of two formulations of 9-hydroxy-risperidone palmitate.

Investigators and study sites: (b) (4)

Trail period: Clinical Conduct: May 29, 1998 to April 27, 1999.

Subjects: 29 subjects. The subjects were male or female subjects aged 18 to 65 years, with diagnosis of schizophrenia.

Study Design: This is a pilot, open label, single dose parallel study. This trial was designed to evaluate the safety, tolerability and pharmacokinetic profile of a single intramuscular injection of two depot formulations (F2 and F4) of 9-hydroxy-risperidone palmitate (R092670) in an aqueous suspension. These F2 and F4 formulations contained particles with specific surface areas (SSA) of 13 m^2/g and 9.5 m^2/g, respectively. These formulations were first evaluated at a dose of 50 mg 9-hydroxy-risperidone-eq. (R076477) in eight (F2) and seven (F4) schizophrenic subjects. Based on interim results of the plasma concentration-time profile, the F4 formulation was selected to be investigated at higher single doses (100 and 150 mg) in two additional groups of seven subjects.

During the trial subjects were allowed to receive or continue other anti-psychotic therapy (except risperidone) as judged appropriate by the investigator. Plasma concentrations of 9-hydroxy-risperidone (R076477), cardiovascular and laboratory safety and tolerability of the formulations were investigated over a period of 12 weeks. After this period, follow-up samples were collected monthly until 9-hydroxy-risperidone plasma levels dropped below 1.0 ng/ml. These plasma concentrations were measured using a validated radioimmunoassay method with a lower limit of quantification of 0.2 ng/ml.

In total, 21 venous blood samples (6 ml each; 126 ml in total) for the determination of drug concentrations in plasma were taken from an arm vein during the 12-week trial. Blood samples were taken before and 1, 2, 4, 8 hours post dose on the day of intramuscular injection (i.e., day 1 of trial). Furthermore, blood samples were drawn at the same time of the day as the time of the R092670 depot injection on trial days 2, 3, 5, 8, 11, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78 and 85 days after the intramuscular injection. Monthly blood sampling was continued (if possible) until the bioanalysis results indicated that the 9-hydroxy-risperidone levels had dropped below 1 ng/ml.

Results:

The pharmacokinetic parameters are shown in the following table.

Parameter	n	Mean ± SD	Median	Min	Max
F2 formulation, 50 mg-eq. R076477					
C_{max}, ng/ml	6	17.3 ± 9.1	15.5	9.62	34.5
t_{max}, days	6	7.2 ± 3.7	7.0	4.0	14.0
$AUC_{85\ days}$, ng.h/ml	6	13239 ± 2075	12684	10936	16358
$t_{1/2\ term}$, days	6	33.7 ± 17.9	29.5	11.3	62.2
AUC_{∞}, ng.h/ml	6	16198 ± 3420	15299	12245	20479
F4 formulation, 50 mg-eq. R076477					
C_{max}, ng/ml	7	12.2 ± 4.6	11.0	5.36	18.4
t_{max}, days	7	10.0 ± 6.0	10.0	4.0	21.0
$AUC_{85\ days}$, ng.h/ml	7	9735 ± 2213	10244	5821	12653
$t_{1/2\ term}$, days	7	30.9 ± 8.5	29.1	23.3	47.5
AUC_{∞}, ng.h/ml	7	11247 ± 2006	11542	7626	13999
F4 formulation, 100 mg-eq. R076477					
C_{max}, ng/ml	7	21.4 ± 12.3	19.8	9.13	44.4
t_{max}, days	7	12.3 ± 11.8	7.0	2.0	35.1
$AUC_{85\ days}$, ng.h/ml	7	17074 ± 5814	17951	9506	23975
$t_{1/2\ term}$, days	5	33.8 ± 18.7	28.6	15.0	60.7
AUC_{∞}, ng.h/ml	5	22278 ± 5384	19866	16863	29966
F4 formulation, 150 mg-eq. R076477					
C_{max}, ng/ml	7	32.5 ± 16.7	29.7	14.6	63.4
t_{max}, days	7	12.9 ± 10.3	10.0	4.0	35.1
$AUC_{85\ days}$, ng.h/ml	7	31146 ± 8915	29673	18722	46392
$t_{1/2\ term}$, days	5	26.3 ± 8.0	21.7	19.5	38.0
AUC_{∞}, ng.h/ml	5	34549 ± 4732	35977	29188	39125

Comments: The results of the trial demonstrate that the F2 formulation displayed the higher release rate and hence the higher peak plasma levels and the lower tmax values. F4 was therefore selected to be administered at higher doses of 100 and 150 mg-eq. R076477. Over the dose range of 50 to 150 mg R076477-eq., peak plasma concentrations and AUC values increased dose-proportionally. The terminal elimination half-life was on average about 30 days, and was consistent over the three dose levels (F4 formulation) and among formulations F2 and F4. Based on the results of the present study, F4 is a suitable injectable depot formulation for monthly administration.

11. Multiple dose study using formulation F4 (R092670-BEL-4)

Study Title: An open, multiple-dose trial in chronic schizophrenic subjects to explore the pharmacokinetics, tolerability and safety following 4-6 consecutive monthly intramuscular injections of a depot formulation of 9-hydroxy-risperidone palmitate (R092670).

Objective: to explore the multiple-dose pharmacokinetics and dose-proportionality of a depot formulation F4 of 9-hydroxy-risperidone palmitate. In addition, tolerability, safety and efficacy were documented.

Investigators and study sites: 10 investigators in multiple centers in Belgium.

Trail period: November 6, 1998 to Augustus 28, 2000.

Subjects: 54 subjects. The subjects were male or female subjects aged 18 to 65 years, with diagnosis of schizophrenia.

Study Design: This is an open, multiple-dose trial in 3 groups of 18 subjects, receiving 4-6 monthly intramuscular injections of R092670 containing 50, 100 or 150 mg-eq. of 9-hydroxy-risperidone. 4-6 injections (alternated between both buttocks) with either 50, 100 or 150 mg-eq. 9-hydroxy-risperidone (i.e., 0.5, 1.0 or 1.5 mL of the aqueous suspension, respectively) as shown below.

- 4 x 50 mg-eq.: 4 monthly injections of 50 mg-eq. 9- hydroxy-risperidone as palmitate ester (R092670) (on Days 1, 29, 57 and 85) (n=6).

- 6 x 50 mg-eq.: 6 monthly injections of 50 mg-eq. 9- hydroxy-risperidone as palmitate ester (R092670) (on Days 1, 29, 57, 85, 133 and 141) (n=12).

- 6 x 100 mg-eq.: 6 monthly injections of 100 mg-eq. 9- hydroxy-risperidone as palmitate ester (R092670) (on Days 1, 29, 57, 85, 133 and 141) (n=18).

- 6 x 150 mg-eq.: 6 monthly injections of 150 mg-eq. 9- hydroxy-risperidone as palmitate ester (R092670) (on Days 1, 29, 57, 85, 133 and 141) (n=18).

Blood samples were taken based on the following schedules.

- Injection 1 (Day 1): immediately before (pre-dose) and at 8, 24, 48, 72 and 96 hours after the 1st injection, and on Day 8, 11, 15 and 22 of the trial.
- Injection 2 (Day 29): immediately before (pre-dose) and on Day 36.
- Injection 3 (Day 57): immediately before (pre-dose) and on Day 64.
- Injection 4 (Day 85): immediately before (pre-dose) and at 8, 24, 48, 72 and 96 hours after the 4th injection and on Day 92, 95, 99, 106, 113, 127, 141, 155 and 169 of the trial.

- Injection 5 (Day 113): immediately before (pre-dose).
- Injection 6 (Day 141): immediately before (pre-dose) and at 8, 24, 48, 72 and 96 hours after the 6th injection and on Day 148, 151, 155, 162, 169, 183, 197, 225 and 253 of the trial.

Results:

The pharmacokinetic parameters are shown in the following table.

Summary of the pharmacokinetic parameters of 9-hydroxy-risperidone (medians)

PARAMETER		DOSE GROUP			
First injection (dose)		50 mg-eq. (N=17)		100 mg-eq. (N=17)	150 mg-eq. (N=18)
C_{max}	ng/mL	12.3		20.2	20.7
T_{max}	h	335.82		239.92	335.48
t_{max}	days	14		10	14
AUC_{τ}	ng.h/mL	5185		8141	10707
Last injection (dose)		4 x 50 mg-eq. (N=6)	6 x 50 mg-eq. (N=9)	6 x 100 mg-eq. (N=17)	6 x 150 mg-eq. (N=18)
C_{min}	ng/mL	9.47	13.2	19.1	31.7
C_{max}	ng/mL	17.8	22.6	44.3	67.5
t_{max}	h	95.87	96.65	95.68	131.68
t_{max}	days	4	4	4	5
AUC_{τ}	ng.h/mL	9670	11302	21568	32464
dn-AUC_{τ}*	ng.h/mL	19339	22604	21568	21642
λ_z	h^{-1}	0.000733	0.000740	0.000945	0.000807
$t_{½term}$	h	945.05	956.48	734.91	861.50
$t_{½term}$	days	39	40	31	36
C_{max}/C_{min}		2.11	1.78	1.74	1.92
$C_{ss,av}$	ng/mL	14.4	16.8	32.1	48.4
R_{ac}		1.71	2.35	2.75	3.56
FI	%	71.3	55.1	62.0	66.5

* Normalized to a dose of 100 mg-eq..
4 x 50 mg-eq.: 4 monthly injections of 50 mg-eq. 9-hydroxy-risperidone as palmitate ester (R092670).
6 x 50 mg-eq.: 6 monthly injections of 50 mg-eq. 9-hydroxy-risperidone as palmitate ester (R092670).
6 x 100 mg-eq.: 6 monthly injections of 100 mg-eq. 9-hydroxy-risperidone as palmitate ester (R092670).
6 x 150 mg-eq.: 6 monthly injections of 150 mg-eq. 9-hydroxy-risperidone as palmitate ester (R092670).

Median pre-dose concentrations

DAY	(week)	9-hydroxy-risperidone pre-dose concentration (ng/mL)		
		4 or 6 x 50 mg-eq.	6 x 100 mg-eq.	6 x 150 mg-eq.
29	(week 5)	5.32	10.3	13.1
57	(week 9)	11.5	18.2	22.3
85	(week 13)	12.7	19.3	27.9
113	(week 17)	10.9	20.6	27.5
141	(week 21)	14.0	22.5	33.1
169	(week 25)	16.7	22.6	35.8

4 or 6 x 50 mg-eq.: 4 or 6 monthly injections of 50 mg-eq. 9-hydroxy-risperidone as palmitate ester (R092670).
6 x 100 mg-eq.: 6 monthly injections of 100 mg-eq. 9-hydroxy-risperidone as palmitate ester (R092670).
6 x 150 mg-eq.: 6 monthly injections of 150 mg-eq. 9-hydroxy-risperidone as palmitate ester (R092670).

Overall, 42 subjects reported at least one adverse event (overall: 114 adverse events). Adverse events reported in at least 3 subjects of the total sample were: bronchitis, rhinitis, tooth disorder, abdominal pain, coughing, pharyngitis, headache, depression and upper respiratory tract infection. The majority of the adverse events were considered to be of mild or moderate severity and not drug-related. None of the subjects died. Four subjects reported serious adverse events; they were hospitalized for various reasons (abnormal hepatic function, renal calculus, confusion/pneumonia and bronchospasm/post-operative pain/aggravated bronchospasm), but no action was taken regarding the trial medication.

Comments:

Steady state was reached after 4 to 5 monthly injections in all dose groups. The pharmacokinetics of the R092670 depot formulation (F4) at steady state are linear over the dose range studied (50 – 150 mg-eq.). The median peak to trough variation ranged from 1.7 to 2.1. The median ratio between the last and the first injection (Rac) ranged from 1.7 to 3.6. The median terminal half-life ranged from 31 to 40 days. The results of the present trial demonstrate that the R092670 depot formulation (F4) was safe in doses of up to 6 injections with 150 mg-eq. 9-hydroxy-risperidone. No significant difference was found between the randomization groups with respect to local tolerability, except for redness, which was more frequently reported with the higher doses (100- and 150 mg-eq.). No consistent changes in cardiovascular safety parameters (ECG and vital signs) and laboratory safety parameters were observed.

12. Single dose study using formulation F11 (R092670-INT-12)

Study Title: Pharmacokinetics, tolerability and safety of 9-hydroxy-risperidone after a single intramuscular injection of the depot formulation of 9-hydroxy-risperidone in schizophrenic volunteers.

Objective: to document the pharmacokinetic profile of 9-hydroxy-risperidone (R076477, paliperidone) and its palmitate ester (R092670) after a single i.m. injection of the R092670 depot formulation at 25, 50, 100, and 150 mg-eq. paliperidone in subjects with schizophrenia and to document the tolerability and the safety of this formulation. Additionally, the disposition of the enantiomers of paliperidone was documented.

Investigators and study sites: (b) (4)

Trail period: Clinical Conduct: May 3, 2001 - December 14, 2001 Sample Analysis: Oct 29, 2001 –Jan 11, 2002

Subjects: 48 subjects. The subjects were male or female subjects aged 18 to 65 years, with diagnosis of schizophrenia.

Study Design: This is a single-dose, open-label, parallel-group Phase 1 study in 48 subjects with schizophrenia. Subjects were allocated to 1 of the 4 treatment groups (A, B, C, or D) by the investigator, based on his clinical judgment.

- Group A: 25 mg-eq. paliperidone;
- Group B: 50 mg-eq. paliperidone;
- Group C: 100 mg-eq. paliperidone;
- Group D: 150 mg-eq. paliperidone.

Blood samples for determination of R076477, its enantiomers (R078543 and R078544), and R092670 concentrations in plasma were taken at predose, and at 1, 4, and 8 hours postdose on the day of the i.m. injection (Day 1), and at approximately the same time of the injection on Days 2, 3, 5, 8, 11, 13, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, and 85 after the i.m. injection. Urine samples for determination of creatinine clearance were collected at predose, and during the following intervals after the i.m. injection: 0-4, 4-8 and 8- 24 hours.

Results:

Enantiomers of paliperidone (R078543 and R078544) and paliperidone palmitate (R092670) plasma levels were determined using LC-MS/MS method. The following table shows the assay performance.

Species	LLOQ	Range	QC samples		Calibration standards	
	(ng/mL)	(ng/mL)	Accuracy (%)	Precision (CV%)	Accuracy (%)	Precision (CV%)
R092670	0.20	0.2-200	-17.0 to 10.0	0.0 to 8.8	-0.7 to 0.7	1.9 to 6.1
R078543	0.20	0.2-100	-14.4 to 11.1	0.0 to 12.1	-3.2 to 3.7	2.0 to 3.7
R078544	0.20	0.2-100	-10.6 to 11.1	0.0 to 13.1	-1.9 to 2.2	1.7 to 3.6

Plasma concentrations of paliperidone palmitate (R092670) could only be assessed for 1 subject (100 mg group) at a single timepoint on Day 1, and for 4 subjects (150 mg group) at a few time points on Day 1 and 2. The highest value measured for R092670 was 0.56 ng/mL.

Plasma concentrations of paliperidone (R076477) increased gradually, and reached median peak plasma levels of 6.8, 4.5, 13.2, and 18.5 ng/mL, respectively between 11.5 to 21.0 days after dosing. The 25-mg and 50-mg dose group were not different from each other. The plasma levels declined with a median half-life between 38 and 47 days over the 3 higher dose levels, and lower at the 25-mg-eq. dose (median half-life 20 days). Detectable levels could be observed in all subjects throughout the complete observation period of 85 days. The pharmacokinetic parameters are shown in the following table.

25 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	28.5 ± 24.7	21.0	4.0	84.0
C_{max}, ng/mL	12	6.47 ± 4.26	6.80	1.66	13.7
AUC_{last}, ng.h/mL	12	5641 ± 3994	4576	1884	14169
$t_{1/2\ term.}$, days	12	22.4 ± 9.9	20.0	10.7	43.1
AUC_{∞}, ng.h/mL	12	6987 ± 4773	5265	1984	16157
50 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	24.1 ± 19.7	14.0	10.0	77.0
C_{max}, ng/mL	12	5.66 ± 3.11	4.45	1.91	12.4
AUC_{last}, ng.h/mL	12	5728 ± 2716	5619	1845	10979
$t_{1/2\ term.}$, days	10	49.7 ± 27.4	40.5	17.5	97.1
AUC_{∞}, ng.h/mL	10	8359 ± 3572	7593	2185	14863
100 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	22.4 ± 14.3	17.8	7.0	49.0
C_{max}, ng/mL	12	16.3 ± 9.6	13.2	4.81	33.2
AUC_{last}, ng.h/mL	12	15813 ± 10835	13127	3959	39102
$t_{1/2\ term.}$, days	7	39.8 ± 19.1	37.6	13.3	64.4
AUC_{∞}, ng.h/mL	7	26789 ± 16089	19489	12691	51981
150 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	18.9 ± 20.1	11.5	2.0	70.0
C_{max}, ng/mL	12	22.9 ± 17.2	18.5	6.33	70.4
AUC_{last}, ng.h/mL	12	22226 ± 22338	17047	4780	91206
$t_{1/2\ term.}$, days	10	50.8 ± 24.2	47.4	20.0	91.9
AUC_{∞}, ng.h/mL	10	35480 ± 31111	22496	17939	121261

Note $t_{1/2term}$: terminal half-life

The exposure to the (+)-enantiomer R078543 was almost twice as high as the exposure to the (-)-enantiomer R078544.

A summary of the pharmacokinetic parameters of the (+)-enantiomers of paliperidone (R078543) is presented in Table below.

25 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	27.6 ± 25.2	17.5	4.0	84.0
C_{max}, ng/mL	12	4.26 ± 2.86	4.79	1.10	9.18
AUC_{last}, ng.h/mL	12	3607 ± 2604	2851	1178	8947
$t_{1/2\ term.}$, days	12	26.1 ± 7.6	25.4	17.3	42.8
AUC_{∞}, ng.h/mL	12	4558 ± 3118	3472	1475	10158
50 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	24.1 ± 19.7	14.0	10.0	77.0
C_{max}, ng/mL	12	3.57 ± 1.90	2.89	1.20	7.46
AUC_{last}, ng.h/mL	12	3611 ± 1684	3636	1233	6567
$t_{1/2\ term.}$, days	8	49.3 ± 32.7	39.1	17.8	113
AUC_{∞}, ng.h/mL	8	5305 ± 1296	4897	3391	6974
100 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	22.4 ± 14.3	17.8	7.0	49.0
C_{max}, ng/mL	12	10.4 ± 6.0	8.67	2.97	21.1
AUC_{last}, ng.h/mL	12	10071 ± 6899	8264	2402	24744
$t_{1/2\ term.}$, days	8	39.4 ± 18.1	36.4	13.3	68.7
AUC_{∞}, ng.h/mL	8	16901 ± 9355	14017	7837	32745
150 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	17.8 ± 21.1	8.5	2.0	70.0
C_{max}, ng/mL	12	14.5 ± 11.2	11.9	3.56	46.2
AUC_{last}, ng.h/mL	12	14071 ± 14880	10525	3009	60074
$t_{1/2\ term.}$, days	9	58.8 ± 36.8	41.3	20.9	122
AUC_{∞}, ng.h/mL	9	23231 ± 22405	13550	10310	81164

A summary of the pharmacokinetic parameters of the (-)-enantiomers of paliperidone (R078544) is presented in Table below.

25 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	22.5 ± 17.7	17.5	4.0	56.0
C_{max}, ng/mL	12	2.24 ± 1.42	2.17	0.56	4.53
AUC_{last}, ng.h/mL	12	2026 ± 1402	1717	686	5226
$t_{1/2\ term.}$, days	12	43.6 ± 45.7	27.4	15.6	181
AUC_{∞}, ng.h/mL	12	2706 ± 1543	2265	1203	6003
50 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	18.4 ± 10.1	14.0	10.0	42.0
C_{max}, ng/mL	12	2.10 ± 1.21	1.61	0.74	4.91
AUC_{last}, ng.h/mL	12	2116 ± 1060	2023	595	4410
$t_{1/2\ term.}$, days	8	51.2 ± 29.2	44.9	17.1	96.5
AUC_{∞}, ng.h/mL	8	3133 ± 1122	2747	1932	4910
100 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	22.4 ± 14.3	17.8	7.0	49.0
C_{max}, ng/mL	12	5.93 ± 3.54	4.46	1.84	12.1
AUC_{last}, ng.h/mL	12	5743 ± 3948	4763	1411	14384
$t_{1/2\ term.}$, days	9	63.1 ± 58.4	40.2	12.6	205
AUC_{∞}, ng.h/mL	9	9567 ± 5430	7152	4463	18815
150 mg-eq. dose group	n	mean ± SD	median	min	max
t_{max}, days	12	19.9 ± 19.4	14.0	4.0	70.0
C_{max}, ng/mL	12	8.63 ± 6.04	6.98	2.40	24.2
AUC_{last}, ng.h/mL	12	8152 ± 7468	6340	1771	31129
$t_{1/2\ term.}$, days	9	58.3 ± 34.5	46.6	18.4	105
AUC_{∞}, ng.h/mL	9	13312 ± 10322	9626	8128	40234

Based on the limited information available from this trial there is no indication of a relationship between paliperidone pharmacokinetic parameters and metabolizer status.

There was no clear relationship between the concentrations of R076477 in plasma and creatinine clearance, or between total clearance and creatinine clearance.

Six out of 48 subjects had detectable (i.e., >0.20 ng/mL) risperidone plasma concentrations at 1 (4 subjects) or more (2 subjects) time points during the study. The highest concentration observed was 1.11 ng/mL. For none of these subjects concomitant risperidone intake was recorded in the CRF. Investigation is ongoing.

In total, 7 (58.3%), 8 (66.7%), 5 (41.7%), and 9 (75.0%) subjects had adverse events after the i.m. injection of R092670 depot formulation containing 25, 50, 100, and 150 mg-eq. paliperidone, respectively. The most frequently reported adverse events were tachycardia (n=9), rhinitis, arthralgia (n=4), insomnia (n=3), anxiety, nervousness, somnolence, bronchitis, coughing, toothache, condition aggravated, fever, and rash (n=2). The majority of the adverse events reported in this study were judged not or doubtfully related to the study medication by the investigator. One severe depression was reported as a serious adverse event. There were no deaths. None of the subjects discontinued the study prematurely due to an adverse event. Three subjects experienced serious adverse events due to a worsening of schizophrenia or comorbid conditions leading to hospitalization and were considered by the investigator to be not or doubtfully related to the study medication.

Comments:

1. Following a single i.m. injection with the F11 formulation of R092670 at a dose of 25, 50, 100 and 150 mg-eq. paliperidone, the plasma concentrations of paliperidone gradually increased to reach peak levels between 11.5 to 21.0 days after dosing. The pharmacokinetic parameters Cmax and AUC tended to increase with dose. The F11 formulation showed similar tmax, lower Cmax and AUClast (at 85 days) and a longer half-life compared to the F4 formulation, which indicates that the release period for F11 is longer than for F4.
2. The exposure to the (+)-enantiomer R078543 was almost twice as high as the exposure to the (-)-enantiomer R078544.

13. Population PK study

Study Title: Population Pharmacokinetics of Paliperidone Palmitate

Objective:
(1) To describe the PK of paliperidone after i.m. administration of its palmitate ester at various doses and from two different injection sites, i.e. deltoid and gluteal muscle;
(2) To obtain estimates of typical PK parameters of paliperidone in the target population and of their inter- and intra-individual variability;
(3) To evaluate the effects of subjects' demographic characteristics and other injection-related covariates on paliperidone PK;
(4) To use simulations for assessing the impact of the statistically significant covariates from the population PK analysis on the overall exposure of paliperidone after i.m. injection of its palmitate ester; and
(5) To perform simulations to support the recommended initiation treatment on Day 1 and 8 with 100 mg eq. deltoid doses using a longer 1.5-inch needle for deltoid injection in heavier subjects (=90 kg) that may allow attainment of potential therapeutic concentrations more quickly.

Methods:
The analysis included pooled data from 1,795 subjects from six Phase 1 trials (R092670-USA-3, R092670-INT-11, R092670-INT-12, R092670-PSY-1001, R092670-PSY-1002, and R092670-PSY-1004) and five Phase 2 and 3 trials (R092670-SCH-201, R092670-PSY-3002, R092670-PSY-3003, R092670-PSY-3004, and R092670-PSY-3005). A total of 18,530 PK samples with valid concentration time-points were available for this analysis.

Nonlinear mixed effects modeling of the pooled data was conducted using NONMEM®. 15,754 (85.0%) PK samples were used to develop the population PK model from 1,401 (78.1%) subjects from nine trials and this was referred to as the index dataset. Several different structural models were tested using log-transformed data (both sides transformed) to evaluate their fit to the data. Inter-individual variability (IIV) was explored for each of the PK parameters in the model, and various residual error models were evaluated to obtain the best fit to the data. Since the plasma concentrations were log-transformed, the residual error was modeled using an additive model. Using the base structural model, the relationships between subject covariates and PK parameters were explored to explain IIV.

The final model, including all significant subject covariates, was then subjected to external validation to assess accuracy and precision. The model was validated using an external dataset that consisted of data from trials R092670-PSY-1002 and R092670-PSY-3002. The validation dataset consisted of 394 (21.9%) subjects that contributed 2,776 (15.0%) plasma samples. Once the population PK model was validated the index and validation datasets were combined and the final model was re-run on the full dataset. Finally, model based simulations were performed to support the recommended dosing

regimens and to assess the potential clinical relevance of identified covariate effects on PK in schizophrenic subjects receiving paliperidone palmitate.

Results:

Different structure models tested are shown below.

A one-compartment model with 1st order elimination best described the PK of paliperidone following i.m. administration of its palmitate ester. The absorption of paliperidone palmitate was complex and based on a deconvolution analysis, a dual input model was specified to best capture this complexity. The absorption component of the model allowed a fraction of the dose to enter relatively quickly into the central compartment via a zero order process. After a certain lag-time the remaining fraction then entered the systemic circulation via a 1st order process. The model can be depicted as follows:

(b) (4)

IIV in clearance (CL), central volume of distribution (V), and the absorption rate constant (KA) was described using an exponential error model. These were estimated at 40%, 69%, and 59% coefficient of variation (CV), respectively, in the final model. The IIV on the splitting fraction (F2) for paliperidone absorption via the dual input process was fitted through logit-transformation and its standard deviation (SD) was 0.064. Similarly, the inter-occasion variability (IOV) on CL, V, and F2 were 26% CV, 14% CV, and 0.07 SD respectively. An additive error model was used to describe the residual variability and its SD was 0.22.

Evaluation of subject covariates demonstrated that absorption-related parameters depended both on subject demographic characteristics and on injection-related covariates. The influence of gender, age, injection volume (IVOL), and injection site (INJS) on KA was significant. Similarly, gender, body mass index (BMI), needle length (NDLL), INJS and IVOL had a statistically significant influence on F2. Moreover, CL was related to creatinine clearance (CRCL), while V was related to BMI and gender. Following table shows the different models that were tested.

	FOCE: D2 ≠ Alag1 OFV -12099		Hybrid: IIV on ALAG OFV -12970		FOCE: IIV on ALAG OFV -13074		FOCE: THE BASE MODEL OFV -12954	
Parameter	Estimate	Precision	Estimate	Precision	Estimate	Precision	Estimate	Precision
CL (L/hr)	4.65	2.4%	5.14	1.9%	4.92	N/A	5.16	0.98%
V (L)	351	4.3%	356	7.0%	345	N/A	355	0.02%
Ka x 10^3 hr^{-1}	0.465	5.9%	0.637	3.5%	0.621	N/A	0.63	0.80%
ALAG1 (hr)	624	0.4%	320	0.6%	308	N/A	310	0.35%
F2	0.338	2.7%	0.195	2.8%	0.185	N/A	0.188	0.60%
D2	610	0.5%	D2=Alag1		D2=Alag1		D2=Alag1	
IIV CL (CV%)	43%	8.6%	48%	8.1%	47%	N/A	48%	0.9%
IIV V (CV%)	90%	15.0%	91%	11.1%	95%	N/A	90%	5.2%
IIV Ka (CV%)	77%	14.0%	71%	7.7%	72%	N/A	71%	0.1%
IIV Alag1 (CV%)	0 FIX		**5%**	37.2%	**5%**	N/A	0 FIX	
IIV F2 (SD)	0.17	6.1%	0.12	7.0%	0.12	N/A	0.12	3.7%
Sigma (SD)	0.3	6.3%	0.29	5.5%	0.28	N/A	0.29	3.0%

N/A: COVARIANCE step failed

Covariate screening from the stepwise linear regression analysis using S-plus is shown below.

Parameter	Covariates Tested	Significant at $p<0.05$ level with Initial Screening in S-plus®
CL	CTRY, ALT, TB, SEX, RACE, AGE, and BMI	• SEX and ALT • CRCL is in the base reference model based on prior knowledge and ΔOFV
V	CTRY, BMI, AGE, SEX, and RACE	• SEX and BMI
Ka	INJS, NDLL, FORM, CTRY, BMI, AGE, RACE, and SEX	• SEX, AGE, CTRY, and INJS • IVOL is in the base reference model based on prior knowledge and ΔOFV • Africa and N. America separate out statistically from a third combined group that contained Europe + Asia
F2	IVOL, INJS, NDLL, FORM, CTRY, BMI, AGE, RACE, and SEX	• SEX, BMI, NDLL, INJS, and IVOL

The following table shows the full covariate models with different number of occasion effects.

		OCC 1-4 OCC 5-7 removed		All OCC. OCC 5-7 merged		All OCC. OCC 5-7 separate	
Theta #	Parameter	Estimate	Precision (CV%)	Estimate	Precision (CV%)	Estimate	Precision (CV%)
1	CL: Shift factor for Females	0.948	5%	0.947	4%	0.953	4%
2	CL (L/hr)	4.98	3%	4.92	3%	4.9	4%
3	CL - CRCL Power	0.363	34%	0.361	22%	0.365	110%
4	CL - ALT Power	0.0466	64%	0.0538	56%	0.056	110%
5	V: Shift factor for Females	0.764	22%	0.759	10%	0.766	16%
6	V (L)	351	8%	349	5%	350	5%
7	V - BMI Power	0.983	69%	0.976	13%	0.937	150%
8	KA: Shift factor for Females	0.753	8%	0.752	7%	0.76	11%
9	KA: Shift factor for N. America	1.15	6%	1.15	5%	1.15	6%
10	KA: Shift factor for Africa	1.76	12%	1.73	11%	1.75	12%
11	KA: Shift factor for Deltoid Injection	1.24	7%	1.22	4%	1.24	5%
12	KA x 10^3 (hr^{-1})	0.482	7%	0.474	6%	0.469	14%
13	KA: Age Power	0.29	31%	0.283	33%	0.274	91%
14	KA: Injection Volume Exponent	0.357	14%	0.361	24%	0.362	74%
15	ALAG1 or D2 (hr)	420	1%	420	1%	420	1%
16	F2: Shift factor for Females	0.785	6%	0.778	4%	0.783	5%
17	F2: Shift factor for Deltoid Injection	1.3	4%	1.29	3%	1.29	4%
18	F2: Shift factor Deltoid Injection with 1.5 inch needle	1.41	7%	1.44	5%	1.44	6%
19	F2	0.22	4%	0.216	4%	0.216	9%
20	F2: BMI Power	0.52	25%	0.513	16%	0.519	15%
21	F2: Injection Volume Exponent	0.255	13%	0.26	29%	0.261	52%
	IIV CL (CV%)	42%	10%	42%	9%	42%	34%
	IIV V (CV%)	76%	13%	77%	18%	76%	82%
	IIV KA (CV%)	55%	23%	55%	10%	56%	34%
	IIV F2 (SD) †	0.058	51%	0.06	26%	0.06	64%
	IOV CL (CV%)	27%	2%	27%	12%	26%	18%
	IOV V (CV%)	22%	48%	22%	39%	22%	46%
	IOV F2 (SD) †	0.096	25%	0.092	15%	0.094	16%
	Sigma (SD)	0.24	8%	0.24	8%	0.24	9%

Table below summarizes the models tested prior to backward elimination of covariates.

Model Description	OFV‡	Δ OFV‡	Comments
Initial Simple Drug Absorption Models			
KA	-10690		Most basic absorption model
KOSKA	-10977	287	$COV aborted
Types of KOKA model with ALAG1 variants			
KOKA; Alag1≠ D2 (Omega ALAG1: 0 FIX)	-12099	1122	This is the structural model most consistent with deconvolution results
KOKA; Alag1 = D2 (Omega ALAG1: 0 FIX)	-12954	855	This is considered the **Base Model**
KOKA; Alag1 = D2 (ETA on ALAG1)	-13074†	N/A	**$COV aborted**. Took several attempts and not considered further due to instability
KOKA; Alag1 = D2 (ETA on ALAG1) HYBRID Method	-12970†	N/A	Different estimation method so ΔOFV may not be valid. CV% of IIV ALAG1 was 5% and hence fixed to zero
Test IVOL, IOV, and CRCL			
KOKA; IVOL on KA	-13005	51	Allows terminal slope to change with dose
KOKA; IVOL on KA; 4x4 IOV* (Temporarily OCC 5-7 removed)	-14004	999	KA IOV Omega estimate: 2.48E-05
KOKA; IVOL on KA; 3x4 IOV* (Temporarily OCC 5-7 removed)	-14004	0	IOV on KA fixed to zero
KOKA; IVOL on KA; 3x4 IOV; CrCL on CL (Temporarily OCC 5-7 removed)	-14072	68	Incorporates a known physiological variable in the model. The model is referred in the text as the base reference model
Variants of the full covariate model			
Full covariate model; 4 OCC IOV (temporarily OCC 5-7 removed)	-14405	332	Allows evaluation of the impact of the ADVAN approximation for switched injection sites
Full covariate model; 7OCC IOV (Put back OCC 5-7 data)	-15247	842	Gives parameter estimates with poor precision and leads to long run times
Full covariate model; 5 OCC IOV (Put back OCC 5-7 data)	-15315	69	This is the model used as the starting point for backward elimination

* # x # IOV refers to # of occasions in the model and the # of parameters on which IOV was tested

‡ Moving along the OFV column, this metric always decreases and models improve statistically from top to bottom (with the only exceptions being those indicated by †). For any given model, the OFV reported in the preceding row was used as a comparator to compute ΔOFV. If a blank row or †s appear then use the next preceding row to obtain the comparator OFV.

† ΔOFV was not computed because the model was not considered further due to instability or because a different estimation method was used where ΔOFV may not be valid

The following tables show the results of backward covariate elimination.

NDLL	CL	CL	V	V	KA	KA	KA	KA	KA	F2	F2	F2	F2	F2	Reference Model OFV -15315		
Covariate off	SEX	ALT	SEX	BMI	SEX	CTRY1	CTRY3	INJS	AGE	SEX	INJS	NDDL	BMI	IVOL	OFV	Δ OFV	p-value
Run # 1	X														-15313	2	0.13
Run # 2		X													-15311	5	3.3E-02
Run # 3			X												-15303	12	4.2E-04
Run # 4				X											-15296	19	1.3E-05
Run # 5					X										-15296	20	9.4E-06
Run # 6						X									-15306	9	2.2E-03
Run # 7							X								-15306	9	2.5E-03
Run # 8								X							-15286	30	5.4E-08
Run # 9									X						-15303	12	4.1E-04
Run # 10										X					-15259	56	6.6E-14
Run # 11											X				-15260	56	8.7E-14
Run # 12												X			-15287	28	1.3E-07
Run # 13													X		-15271	44	3.4E-11
Run # 14*														X	-15210	105	1.0E-24

* The covariance step was aborted with this run which is not surprising given that this model led to the largest increase in OFV
The cell highlighted in the first row represents the full covariate model which had the reference OFV against which ΔOFV values were computed.
The horizontal highlighted row represents the least important covariate that was dropped from the model.
X represents the covariate that was turned off for that particular run

Parameter	CL	CL	V	V	KA	KA	KA	KA	KA	F2	F2	F2	F2	F2	Reference OFV -15313		
Covariate off	SEX	ALT	SEX	BMI	SEX	CTRY1	CTRY3	INJS	AGE	SEX	INJS	NDLL	BMI	IVOL	OFV	Δ OFV	p-value
Run # 1	X	X													-15307.1	6	1.5E-02
Run # 2	X		X												-15302	11	9.2E-04
Run # 3	X			X											-15293.8	19	1.2E-05
Run # 4	X				X										-15282.6	30	3.5E-08
Run # 5	X					X									-15299.8	13	2.9E-04
Run # 6	X						X								-15308.8	4	0.04
Run # 7	X							X							-15283.5	29	5.7E-08
Run # 8	X								X						-15300.7	12	4.7E-04
Run # 9	X									X					-15264.2	49	2.8E-12
Run # 10	X										X				-15257.1	56	7.8E-14
Run # 11	X											X			-15285.1	28	1.3E-07
Run # 12	X												X		-15269.7	43	4.8E-11
Run # 13	X													X	-15207.8	105	1.1E-24

The cell highlighted in the first row is the model derived from backward elimination step 1. It has the reference OFV against which ΔOFV was computed.
The horizontal highlighted row represents the least important covariate that was dropped from the model during this step
The vertical highlighted column represents the covariate that was dropped from the model during step 1 of backward elimination
X represents the covariate that was turned off for that particular run

Parameter	CL	CL	V	V	KA	KA	KA	KA	KA	F2	F2	F2	F2	F2	Base Model OFV -15309		
Covariate off	SEX	ALT	SEX	BMI	SEX	CTRY1	CTRY3	INJS	AGE	SEX	INJS	NDLL	BMI	IVOL	OFV	Δ OFV	p-value
Run # 1	X	X					X								-15303	6	0.02
Run # 2	X		X				X								-15291	17	3.0E-05
Run # 3	X			X			X								-15285	24	1.0E-06
Run # 4	X				X		X								-15286	23	1.8E-06
Run # 5	X					X	X								-15296	13	3.8E-04
Run # 6	X						X	X							-15283	26	4.2E-07
Run # 7	X						X		X						-15296	13	3.7E-04
Run # 8	X						X			X					-15255	54	2.5E-13
Run # 9	X						X				X				-15246	63	2.2E-15
Run # 10	X						X					X			-15274	35	3.5E-09
Run # 11	X						X						X		-15265	44	4.1E-11
Run # 12	X						X							X	-15188	120	5.3E-28

The cell highlighted in the first row is the model derived from backward elimination step 2. It has the reference OFV against which ΔOFV was computed.
The horizontal highlighted row represents the least important covariate that was dropped from the model during this step
The vertical highlighted column represents the covariates that were dropped from the model during prior backward elimination steps
X represents the covariate that was turned off for that particular run

Parameter	CL	CL	V	V	KA	KA	KA	KA	KA	F2	F2	F2	F2	F2	Base Model OFV -15303		
Covariate off	SEX	ALT	SEX	BMI	SEX	CTRY1	CTRY3	INJS	AGE	SEX	INJS	NDLL	BMI	IVOL	OFV	Δ OFV	p-value
Run # 1	X	X	X				X								-15283	21	5.5E-06
Run # 2	X	X		X			X								-15271	33	1.1E-08
Run # 3	X	X			X		X								-15269	34	5.5E-09
Run # 4	X	X				X	X								-15296	7	0.006
Run # 5	X	X					X	X							-15278	26	4.4E-07
Run # 6	X	X					X		X						-15291	12	4.6E-04
Run # 7	X	X					X			X					-15251	52	5.9E-13
Run # 8	X	X					X				X				-15240	64	1.5E-15
Run # 9	X	X					X					X			-15271	32	1.3E-08
Run # 10	X	X					X						X		-15257	46	1.2E-11
Run # 11	X	X					X							X	-15172	131	2.0E-30

The cell highlighted in the first row is the model derived from backward elimination step 3. It has the reference OFV against which ΔOFV was computed.
The horizontal highlighted row represents the least important covariate that was dropped from the model during this step
The vertical highlighted column represents the covariates that were dropped from the model during prior backward elimination steps
X represents the covariate that was turned off for that particular run

The external validation prediction errors are summarized in the following table.

Prediction error percents (PE%)				
N	Observed Median	Median cut-off to pass validation	Observed 25th percentile	Observed 75th percentile
2760	-4.4	±15	-21.6	14.5

Absolute prediction error percents (|PE|%)				
N	Observed Median	Median cut-off to pass validation	Observed 25th percentile	Observed 75th percentile
2760	18.4	30	8.37	37.3

The equations below describe the relationships between covariates and the typical values (TV) of PK parameters in subject j:

$$TVCLj = 4.95 \bullet \left(\frac{CRCLj}{110.6}\right)^{0.376}$$

where 4.95 L/hr is the TVCL for an individual with CRCL = 110.6 mL/min.

$$TVVj = SEX\_Vj \bullet 391 \bullet \left(\frac{BMIj}{26.8}\right)^{0.889}$$

where SEX_Vj is 1 for males and a shift factor of 0.726 for females; and 391 L is TVV for a male individual with BMI = 26.8 kg/m^2.

$$TVKAj = SEX\_KAj \bullet INJS\_KAj \bullet 0.488 \times 10^{-3} \bullet \left(\frac{AGEj}{42}\right)^{0.311} \bullet IVOLj^{-0.359}$$

where SEX_KAj is 1 for males and a shift factor of 0.765 for females; INJS_KAj is 1 for gluteal injection and a shift factor of 1.23 for the deltoid injection; and 0.488 x 10^{-3} hr^{-1} is the TVKA for a male individual with AGE = 42 yr and 100 mg eq. dose in the gluteal muscle (i.e. IVOL = 1 mL).

$$TVF2j = SEX\_F2j \bullet INJS\_F2j \bullet NDLL\_F2j \bullet 0.168 \bullet \left(\frac{BMIj}{26.8}\right)^{-0.642} \bullet IVOLj^{-0.288}$$

where SEX_F2j is 1 for males and a shift factor of 0.781 for females; INJS_F2j is 1 for gluteal and 1.37 for deltoid injection; NDLL_F2j is 1 for gluteal injection with 1.5-inch needle, 1 for deltoid injection with 1-inch needle, and 1.54 for deltoid injection with 1.5-inch needle; and 0.168 is TVF2 for a male individual with BMI = 26.8 kg/m^2 and 100 mg eq. dose in the gluteal muscle (i.e. IVOL = 1 mL).

The final parameter estimates are shown below.

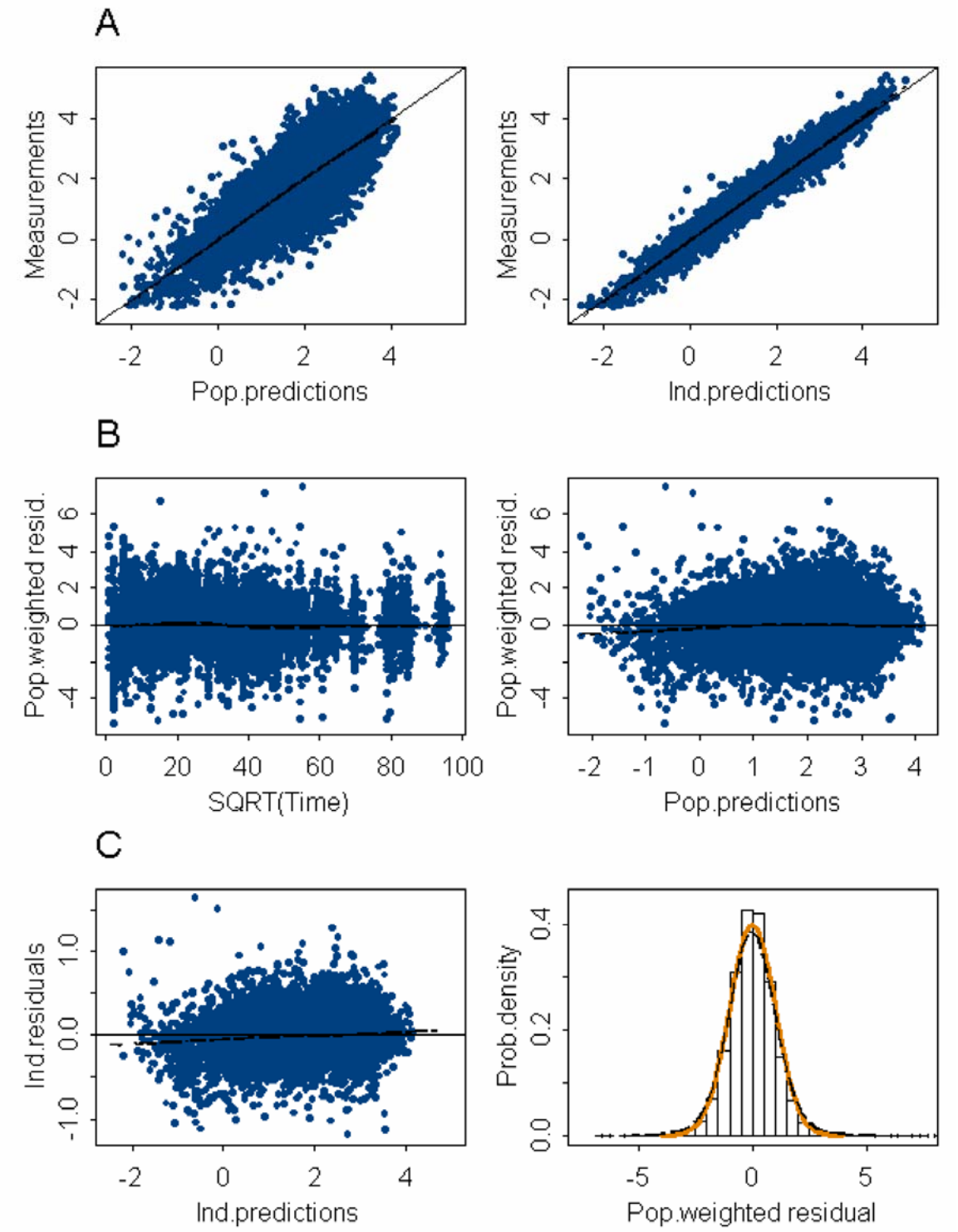
Dataset used		Index + Validation		Index + Validation	
IOV Status		IOV Included		IOV Turned Off	
Number of outliers excluded		54		54	
Theta #	Parameter*	Estimate	Precision	Estimate	Precision
1	CL (L/hr)	4.95	1%	5.1	2%
2	CL - CRCL Power	0.376	3%	0.369	60%
3	V: Shift factor for Females	0.726	8%	0.778	14%
4	V (L)	391	3%	385	6%
5	V - BMI Power	0.889	1%	0.807	56%
6	KA: Shift factor for Females	0.765	7%	0.777	7%
7	KA: Shift factor for Deltoid Injection	1.23	3%	1.18	5%
8	KA x 10^3 (hr^{-1})	0.488	2%	0.558	9%
9	KA: Age Power	0.311	14%	0.349	25%
10	KA: Injection Volume Exponent	0.359	3%	0.308	24%
11	ALAG1 or D2 (hr)	319	1%	316	1%
12	F2: Shift factor for Females	0.781	4%	0.8	4%
13	F2: Shift factor for Deltoid Injection	1.37	3%	1.37	4%
14	F2: Shift factor Deltoid 1.5 inch needle	1.54	6%	1.46	7%
15	F2	0.168	2%	0.171	4%
16	F2: BMI Power	0.642	1%	0.717	8%
17	F2: Injection Volume Exponent	0.288	1%	0.274	18%
	IIV CL (CV%)	40%	2%	45%	11%
	IIV V (CV%)	69%	4%	79%	13%
	IIV KA (CV%)	59%	3%	70%	14%
	IIV F2 (SD) †	0.064	2%	0.098	8%
	IOV CL (CV%)	26%	2%	0 FIX	N/A
	IOV V (CV%)	14%	2%	0 FIX	N/A
	IOV F2 (SD) †	0.07	2%	0 FIX	N/A
	Sigma (SD)	0.22	3%	0.27	3%
	OFV	-20238		-17934	

* For parameter equations refer to the footer in Table 11

† IOV and IIV for F2 is computed for 100 mg eq. gluteal injection for a male subject with BMI of 26.8 kg/m^2

N/A: Not applicable

The goodness-of-fit plots for the final model are shown below.

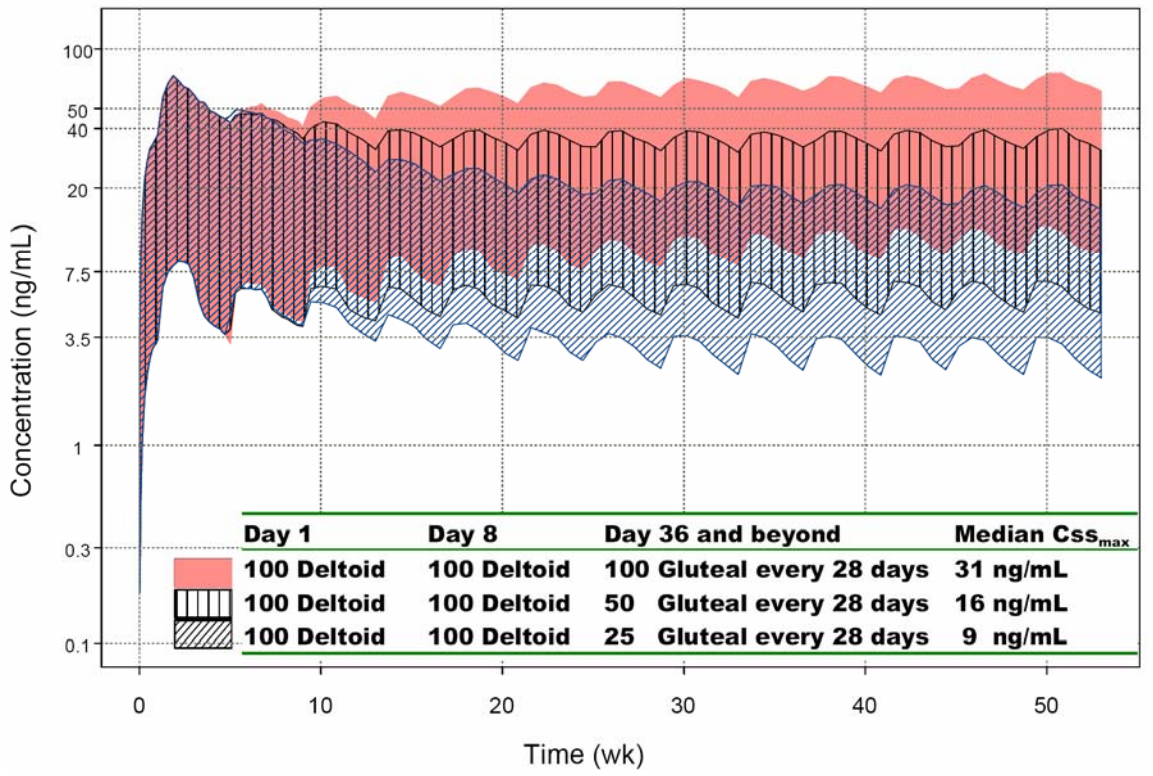


The results thus show that about 17% (F2 is about 0.17) of the administered drug entered the systemic circulation via a relatively fast zero-order input (duration D2=319 hr, which is also equal to the lag time ALAG1). The remaining fraction entered the systemic circulation via the slow first-order process, which governed the apparent half-life of this drug due to flip-flop kinetics. The estimates of CL (which is equal to intravenous

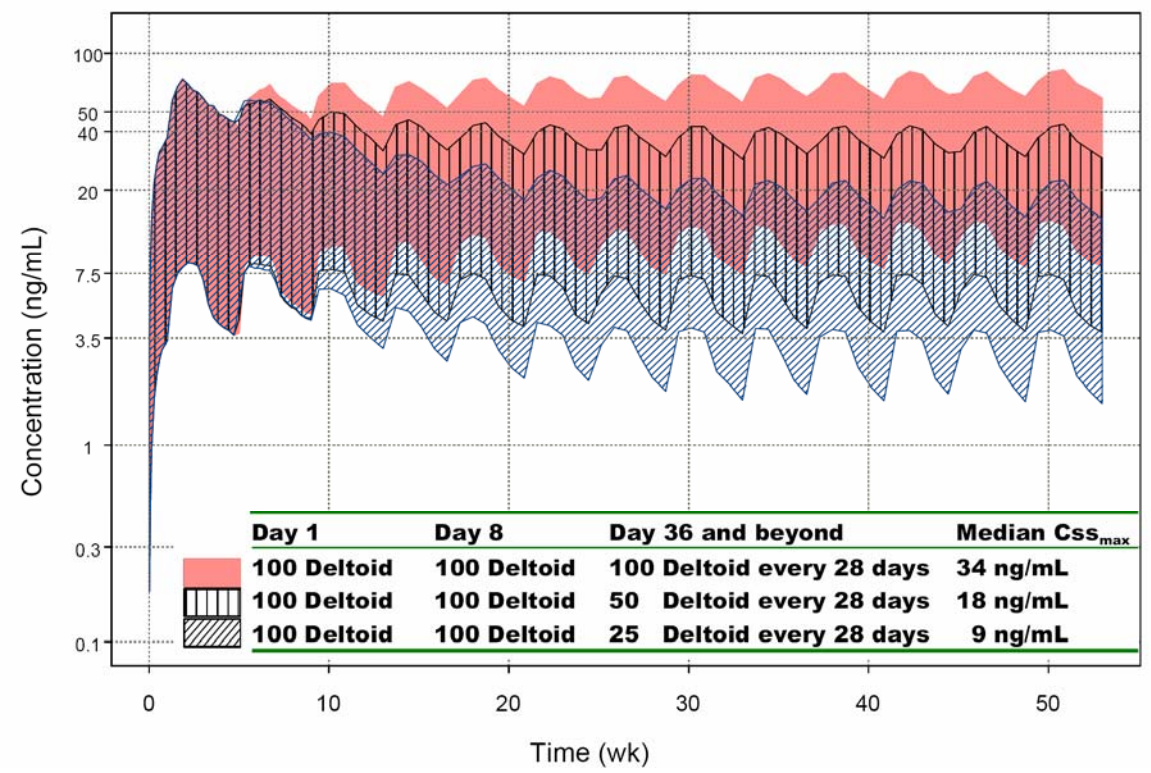
paliperidone CL reported previously) and KA substantiated that paliperidone palmitate offers complete bioavailability and at the same time provides sustained release of paliperidone. Finally, the comparison of two formulations with identical particle sizes, F011 and F013 (used in later clinical development) resulted in very similar PK profiles, and no apparent differences could be detected statistically or visually between the post-hoc parameter values for these two formulations.

Simulation scenarios with the statistically significant covariates from the population PK analysis revealed the following features about paliperidone PK after administration of paliperidone palmitate.

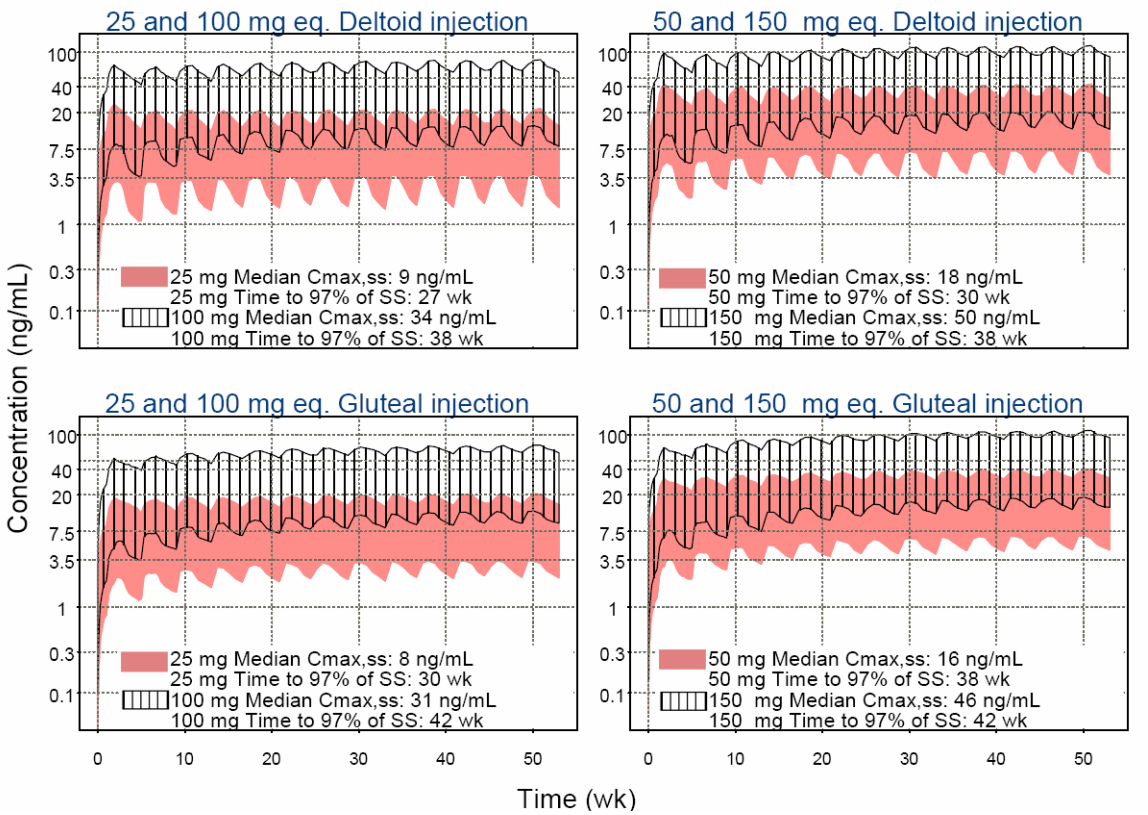
The following figure shows the simulation for the dosing scenario where the injection site is switched from the deltoid to the gluteal muscle after the second injection. The shaded and hatched regions represent the 90% prediction interval.



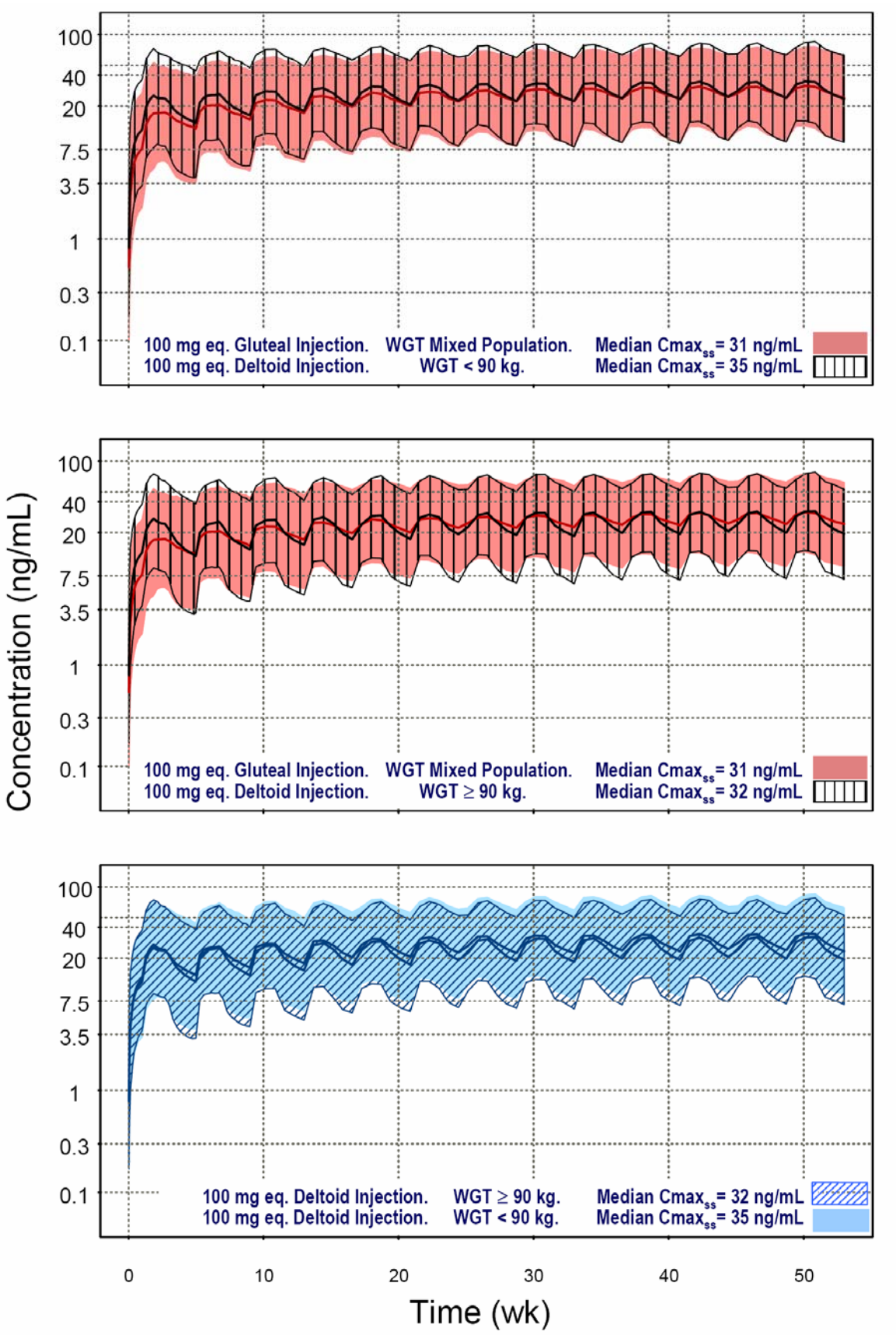
The following figure shows the simulation for the dosing scenario that is identical to the above except that the injection site is not switched after the second injection.



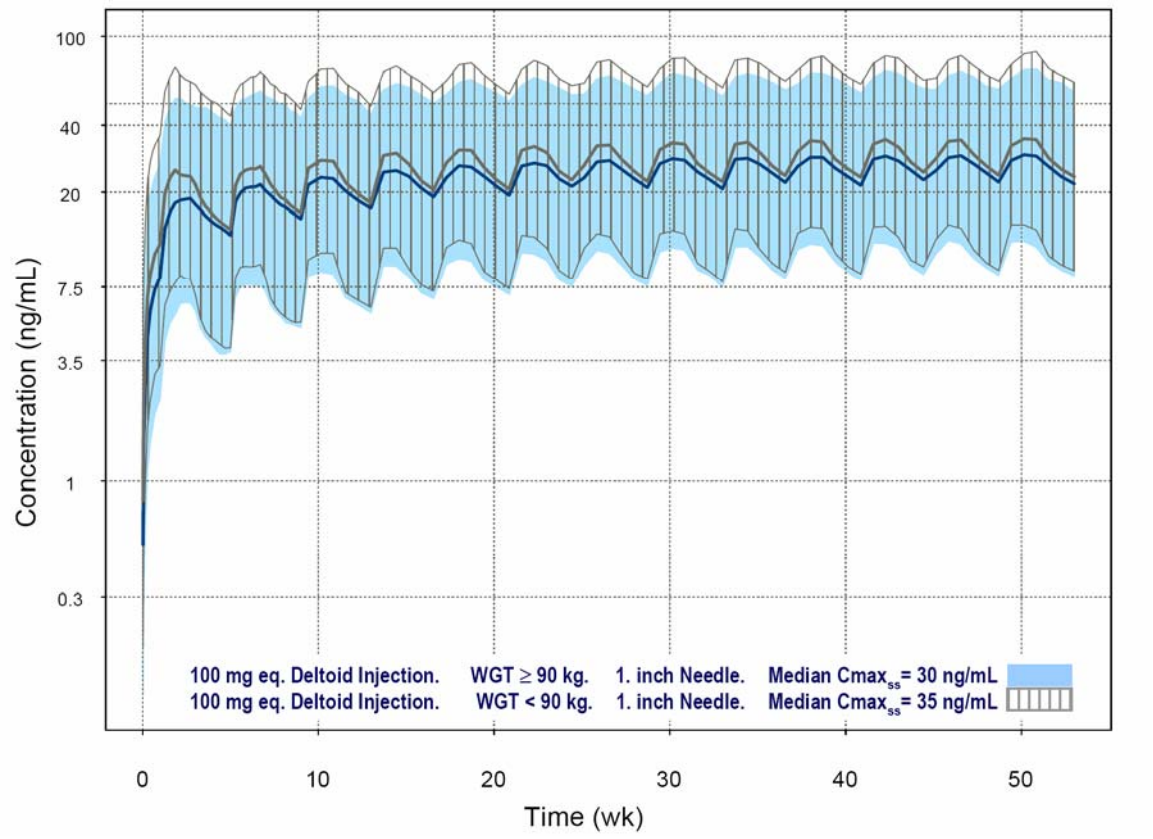
The following figure shows the simulated time to reach steady state for different doses and injection sites.



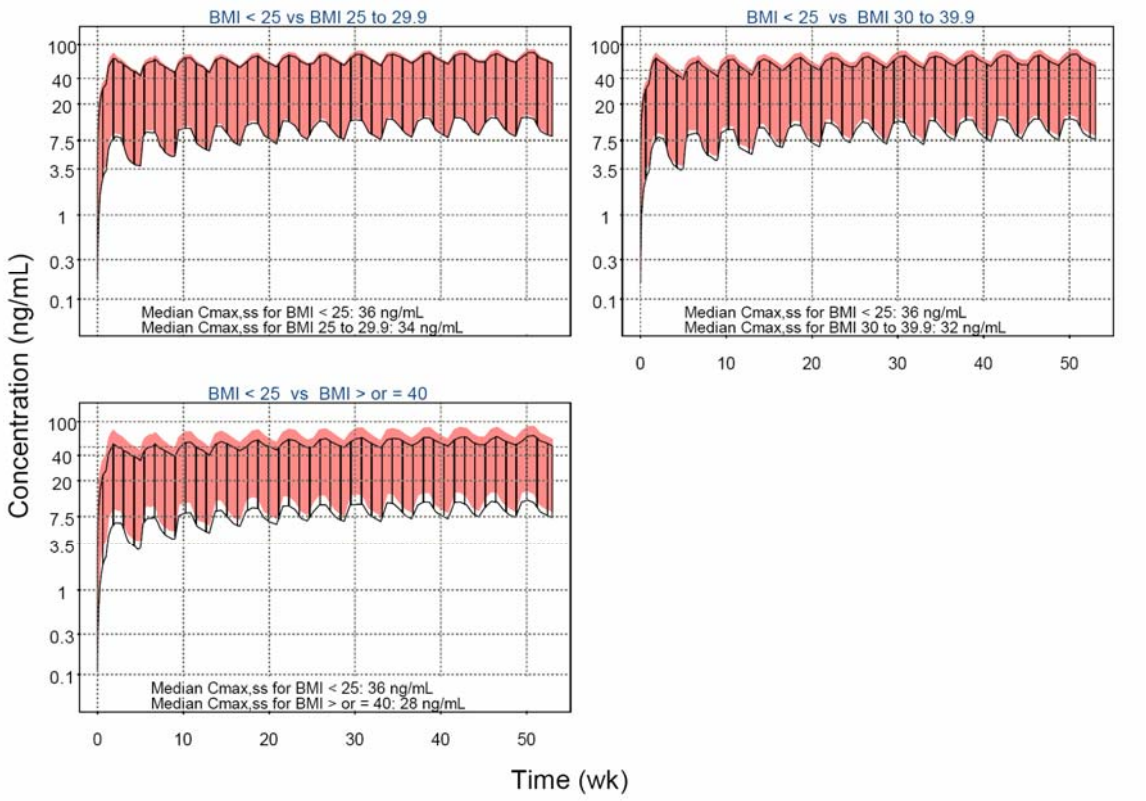
Following figure shows the simulation outcome for the influence of needle length and injection site on PK. The 3 combinations of recommended needle length, WT, and injection site are compared against one another. The shaded areas and lines represent the 90% prediction interval and the median.


100
40
20
7.5
3.5
1
0.3
0.1
100 mg eq. Gluteal Injection.
100 mg eq. Deltoid Injection.
WGT Mixed Population.
WGT < 90 kg.
Median Cmax$_{ss}$ = 31 ng/mL
Median Cmax$_{ss}$ = 35 ng/mL
Concentration (ng/mL)
100 mg eq. Gluteal Injection.
100 mg eq. Deltoid Injection.
WGT Mixed Population.
WGT ≥ 90 kg.
Median Cmax$_{ss}$ = 31 ng/mL
Median Cmax$_{ss}$ = 32 ng/mL
100 mg eq. Deltoid Injection.
100 mg eq. Deltoid Injection.
WGT ≥ 90 kg.
WGT < 90 kg.
Median Cmax$_{ss}$ = 32 ng/mL
Median Cmax$_{ss}$ = 35 ng/mL
0
10
20
30
40
50
Time (wk)

Following figure shows an assessment of a hypothetical scenario where deltoid injections with 1-inch needle for subjects with WGT =90 kg was simulated and compared to the recommended deltoid injections with 1-inch needle for subjects with WGT <90 kg. This comparison assesses of the hypothetical possibility of using a single needle length for deltoid injections across the WGT groups.



The following figures show the simulation results to illustrate the influence of BMI on PK. The 3 Panels Represent the 4 BMI Sub-Groups. Normal BMI subjects (pink solid region) are compared with overweight subjects (top left hatched area), obese subjects (top right hatched area), and morbidly obese subjects (bottom left hatched area). The shaded areas represent the 90% prediction interval.



Comments

- Compared to deltoid injections, repeated administration in the gluteal muscle resulted in a delayed time to achieve steady-state (~ 4 wk longer), but did not influence the overall exposure (in terms of steady-state concentrations) to paliperidone.

- Deltoid injections resulted in a faster rise in initial plasma concentrations, facilitating a rapid attainment of potential therapeutic concentrations. The deltoid injection site is therefore recommended as the initiation site for dosing paliperidone palmitate.

- Higher doses associated with larger injection volumes increased the apparent half-life of paliperidone, which in turn increased the time to achieve steady-state.

- Needle length was an important variable for the absorption kinetics from the deltoid injection-site and it is recommended to use a longer 1.5-inch needle for deltoid administration in heavier subjects (>=90kg). Simulations indicated that the use of a longer needle in the deltoid muscle for the heavy individuals might be associated with an initial faster release of paliperidone into the systemic circulation, which could help overcome the slower absorption observed in heavier individuals described below.

- The body size variable BMI was another important covariate for paliperidone palmitate. A slower rise in initial concentrations was observed in the obese population, which possibly occurred due to the reduced speed of initial influx from the injection site. Initiating the first two injections in the deltoid muscle and using a

longer 1.5-inch needle for deltoid injection in heavy subjects can mitigate this effect. These observations are consistent with the expectation that in heavy subjects, administration into the adipose layer of the deltoid muscle can be avoided with the use of a longer injection needle.

- Renal function was an important covariate influencing the PK of paliperidone. Simulations indicate that a 75 mg eq. dose in subjects with mild renal impairment (CRCL: 50-80 mL/min) resulted in a similar exposure as a 100 mg eq. dose in subjects with normal renal function (CrCL >80 mL/min). This may therefore form the basis for dose adjustment in renally impaired subjects.

- Finally, age (on KA) and gender (on KA, F2, and V) were two subject related variables that were statistically significant in the covariate analysis. However, simulations indicate that their influence on systemic exposure was too small to be of clinical relevance.

14. In vitro study (Study FK5302)

Study title: The *in-vitro* hydrolysis of R092670 in selected tissue fractions of human and the identification of esterase(s) involved in the hydrolysis.

Objective: The *in vitro* ester hydrolysis of paliperidone palmitate (R092670, a racemate) was studied in human liver sub-cellular fractions with and without addition of NADPH system at different concentrations (5 - 3000 ng paliperidone eq./mL). The hydrolysis was also examined in 12,000 *x* g fractions of human kidney and muscle tissue.

Investigators and study sites: Rao N.V.S. Mamidi and Jos Van Houdt. Turnhoutseweg 30, B-2340 Beerse, Belgium. Johnson & Johnson Pharmaceutical Research & Development.

Study design:

In all samples, paliperidone palmitate and the hydrolysis products (paliperidone enantiomers, R078543 (+) and R078544 (-)) were measured by qualified chiral LC-MS/MS methods. The percent hydrolysis of paliperidone palmitate was calculated based on the sum of the released paliperidone enantiomers and the relative role of the different tissues in the hydrolysis was assigned. The hydrolysis was also investigated in plasma and blood of healthy human subjects and plasma samples of hepatic impaired patients. To determine the nature of esterases involved in the hydrolysis, paliperidone palmitate hydrolysis was examined in human liver microsomes, plasma and blood with and without addition of diagnostic esterase inhibitors [paraoxon (1 µM), di-isopropylfluorophosphate (DIFP, 1 µM) for serine esterases; bis(4-nitrophenyl)-phosphate (BNPP, 1 µM) for carboxyl esterases; eserine for cholinesterase and carboxylesterase (100 µM); acetylcholine (100 µM) for acetylcholinesterase; benzoylcholine (100 µM) for pseudocholinesterase; chloral hydrate (10 µM) for retinylpalmitoyl hydrolase]. The percent inhibition by various diagnostic inhibitors was expressed against the hydrolysis observed in control incubations without inhibitor. The ester hydrolysis of paliperidone palmitate increased with incubation time in both microsomes and 12,000 *x* g fractions of the above matrices.

Results:

In general, at the highest concentration (3000 ng/mL) the relative hydrolysis was lower than the lower concentrations (5 – 500 ng/mL). There was no difference in percent hydrolysis with and without NADPH system indicating that oxidoreductase enzymes were not involved. It appears that the extent of hydrolysis was highest (up to 55.2 %) in liver microsomes and liver 12,000 *x* g fractions than in any other matrices tested in this study. The extent of hydrolysis appeared to be moderate (up to 28.3 %) and similar in human muscle and human kidney 12,000 *x* g fractions. A limited fraction of paliperidone palmitate was hydrolyzed (up to 5.4 %) in human blood. The hydrolysis was negligible or undetectable in healthy human and hepatic impaired patient plasma samples. Nearly

complete inhibition of hydrolysis was observed with DIFP in liver microsomes indicating that serine esterases were involved in the hydrolysis. Other inhibitors did show weak to moderate inhibition of hydrolysis and possible role of the respective enzymes in the hydrolysis cannot be ruled out. In blood, both serine esterase inhibitors (DIFP and paraxon) significantly inhibited the hydrolysis, which further substantiates that serine esterases are involved in the hydrolysis of paliperidone palmitate.

Comments

1. The study showed that serine esterases were involved in the hydrolysis of paliperidone palmitate.

16 FILING/REVIEW FORM

16.1.1 Office of Clinical Pharmacology and Biopharmaceutics

17 *New Drug Application Filing and Review Form*

17.1.1.1.1 General Information About the Submission

	Information		Information
NDA Number	**22-264**	**Brand Name**	**TBD (Invega)**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Paliperidone palmitate**
Medical Division	**DPP**	**Drug Class**	**Antipsychotic**
OCPB Reviewer	**John Duan**	**Indication(s)**	**Treatment of Schizophrenia and the prevention of recurrence of schizophrenia**
OCPB Team Leader	**Raman Baweja**	**Dosage Form**	**25, 50, 75 and 100 mg Prefilled Injectable Syringes**
		Dosing Regimen	**Initiate with (b) (4) mg-eq on days 1 and 8, then 25 - 100 mg- eq IM q 4 weeks**
Date of Submission	**10/26/07**	**Route of Administration**	**IM Injection**
Estimated Due Date of OCPB Review	**6/26/08**	**Sponsor**	**Johnson and Johnson**
PDUFA Due Date	**8/26/08**	**Priority Classification**	**Standard**
17.1.1.2 Division Due Date	**6/19/08**		

17.1.1.2.1.1.1.1 Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
17.2 Healthy Volunteers-				
single dose:				
multiple dose:	17.2.1.1.1.1.1			
17.2.2 Patients-				
single dose:	**X**	4		
multiple dose:	**X**	**4**		
Dose proportionality -				
fasting / non-fasting single dose:	**X**			
fasting / non-fasting multiple dose:	**X**	**2**		
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	17.2.2.1.1.1.1			
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	17.2.2.1.1.1.1			
Population Analyses -				
Data rich:				
Data sparse:	X	1		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):	**X**	**1**		
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				
17.2.2.1.1.2		**12**		
17.2.2.1.1.3 Filability and QBR comments				

17.2.2.2	**"X" if yes**	17.2.2.2.1.1.1.1.1 Comments
17.2.2.3 Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
17.2.2.4 Comments sent to firm ? **17.2.2.5**		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	**Is there a difference in PK between injection at the gluteal and deltoid muscle sites?** **Is the recommended dosing regimen for IM administration acceptable?** **Is the exposure after IM similar to that after oral administration?** **Is the pharmacokinetics similar after IM and Oral administration?** **Is there effect of covariates such as BMI on exposure after IM administration?**	
Other comments or information not included above		
Primary reviewer Signature and Date	**John Duan**	
Secondary reviewer Signature and Date	**Raman Baweja**	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Duan
8/1/2008 10:44:38 AM
BIOPHARMACEUTICS

Raman Baweja
8/1/2008 12:20:51 PM
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